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## Review Article

# Cardiovascular And Metabolic Abnormalities Induced By Antipsychotic Drug Therapy And Their Management Strategies

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## ABSTRACT

Cardiovascular disease is the leading cause of death in people with severe mental disorders. Reports of sudden death in patients receiving antipsychotic treatment have raised concerns about the safety of antipsychotic drugs. Antipsychotic medications can induce cardiovascular and metabolic abnormalities (such as obesity, hyperglycemia, dyslipidemia and the metabolic syndrome) that are associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease. The direct, non-specific pharmacological actions of antipsychotic drugs can lead to adverse cardiovascular effects, including orthostatic hypotension, tachycardia and ventricular arrhythmias. Among the second generation antipsychotics, clozapine and olanzapine are associated with the highest risk of substantial weight gain, similar to the weight gain potential associated with low-potency first-generation antipsychotics such as thioridazine or chlorpromazine, as well as with an increased risk of diabetes and dyslipidemia. Despite existing guidelines and recommendations, many antipsychotic-drug-treated patients are not assessed for even the most easily measurable metabolic and cardiac risk factors, such as obesity and blood pressure. This Review outlines the metabolic and cardiovascular risks of various antipsychotic medications and makes recommendations for monitoring of patients taking these agents and specific management strategies.

## INTRODUCTION

Antipsychotics, previously known as neuroleptics and major tranquilizers, are a class of psychotropic medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia but also in a range of other psychotic disorders.

Patients with schizophrenia experience increased morbidity and mortality and have an approximately 20% shorter lifespan. Patients with schizophrenia also have a relatively increased prevalence of cardiometabolic risk factors, such as obesity, type 2 diabetes, hypertension, hyperglycemia, and dyslipidemia. Antipsychotics

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find its main action on dopamine receptors, reducing levels of excess dopamine. They may also affect levels of other neurotransmitters, namely acetylcholine, noradrenaline, and serotonin. First-generation antipsychotics (e.g. chlorpromazine), known as typical antipsychotics, were first introduced in the 1950s, and others were developed until the early 1970s. Second-generation antipsychotics, known as atypical antipsychotics, arrived with the introduction of clozapine in the early 1970s followed by others (e.g. risperidone). Both generations of medication block receptors in the brain for dopamine, but atypicals block serotonin receptors as well. Third-generation antipsychotics were introduced in the 2000s and offer partial agonism, rather than blockade, of dopamine receptors. Typical, or “first-generation” including Chlorpromazine, Haloperidol have a relatively lower affinity for serotonin 5HT<sub>2A</sub> receptors than dopamine D<sub>2</sub> receptors and are more prone to cause extrapyramidal side effects due to their efficacy in blocking D<sub>2</sub> receptors in the striatum. Atypical, or “second-generation” including Olanzapine, clozapine, Risperidone block serotonin 5HT<sub>2A</sub>, as well as dopamine D<sub>2</sub> receptors, With high affinity. Antagonism of 5-HT<sub>2A</sub> receptors disinhibits the release of dopamine in the nigrostriatal pathway and therefore lowers the risk of extrapyramidal symptoms. The extrapyramidal symptoms include acute dyskinesias and dystonic reactions, tardive dyskinesia, Parkinsonism, akinesia, akathisia, and neuroleptic malignant syndrome. However, some antipsychotic drugs have a high tendency to cause weight gain and metabolic abnormalities, therefore increasing the risk of obesity, metabolic syndrome, type 2 diabetes mellitus, dyslipidaemia and cardiovascular disease, Atypical antipsychotics have higher incidence of metabolic and cardiovascular abnormalities. These adverse effects are especially prominent in vulnerable populations, such as patients with a first episode of

schizophrenia, those who have not previously taken antipsychotic agents (drug-naive). Nevertheless, patients receiving antipsychotic treatment, including these especially vulnerable groups, are often insufficiently assessed for cardiovascular and metabolic risk factors. This review outlines the metabolic and cardio vascular risks associated with various antipsychotic drugs and includes recommendations for monitoring and management of these risk in patients with antipsychotic therapy.

## **METABOLIC EFFECTS OF ANTIPSYCHOTICS**

### **Weight gain and obesity**

In the long term, weight gain is a potential problem for many patients receiving antipsychotic therapy. “Clinically significant” weight gain is commonly defined as a  $\geq 7\%$  increase in body weight from baseline. Weight gain is greatest with the second-generation agents in which clozapine and olanzapine are more prevalent compared to others. An increasing body of evidence indicates that, compared with the general population, people with early-stage or previously untreated schizophrenia and bipolar disorder are at an increased risk of overweight (BMI 25–<30 kg/m<sup>2</sup>, Obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) and central obesity (waist circumference >102 cm in men and >88 cm in women; That is, a 2.8–3.5-fold increase in the risk of obesity in patients with schizophrenia and a 1.2–1.5-fold increase in patients with bipolar disorder.(1,2) Moreover, all anti psychotic drugs can cause notable weight gain in patients who are taking these agents for the first time.

Evidence regarding the mechanism(s) underlying antipsychotic-induced weight gain includes studies of the relationship between weight gain and drug interactions with various neurotransmitter receptors. The level of H<sub>1</sub> antagonism and blockade of central 5-HT<sub>2C</sub> associated with different antipsychotic medications is hypothesized to modulate feeding



behaviour (increased appetite and decreased sensation of satiety), based on the significant association of weight gain and the binding affinity for this receptor. Antipsychotics with minimal affinity for H1 receptors, such as aripiprazole, ziprasidone, and haloperidol, are associated with limited weight gain, while antipsychotics with a high affinity for H1 receptors, such as clozapine, olanzapine, and chlorpromazine, are associated with clinically significant increases in weight. neurotransmitter receptors including serotonin 5-HT<sub>2A</sub>, dopamine D<sub>2</sub> and D<sub>3</sub>, histamine H<sub>1</sub> and muscarinic M<sub>3</sub> receptors may be also included. Other mechanisms includes action of antipsychotics on neuropeptides associated with appetite control and energy metabolism. Leptin and adiponectin are the adipokines produced in white adipose tissue, which have been implicated in weight gain. Increased leptin levels and reduced adiponectin levels have been demonstrated with short-term and long-term olanzapine treatment. Ghrelin, which acts on the arcuate nucleus of the hypothalamus to enhance food intake and adipose tissue deposition, is also affected by antipsychotics. Effects of antipsychotics on lipid and glucose metabolism have been linked to their effect on weight gain and adiposity. Genetic polymorphisms may explain the individual variation of antipsychotic induced weight gain. Factors that influence a patient's risk of antipsychotic-drug-induced weight gain include demographic variables, treatment setting (inpatient versus outpatient), illness characteristics, past and current treatment with medications, and the patient's pre-treatment diet, activity levels, and body composition levels, and body composition. There is rapid weight gain in the first few weeks after commencing antipsychotics. The rate of weight gain then gradually decreases and flattens over several months. Time taken to plateau was different for each antipsychotic, ranging from 4 to 9 months for

olanzapine and from 42 to 46 months for clozapine. A switch from a weight gain-inducing antipsychotic (such as olanzapine) to an antipsychotic with a limited risk for weight gain (such as aripiprazole and ziprasidone) would result in reductions in mean weight. Dose reduction of initial drug can also be opted if possible. Moreover every interventions that result in weight loss can improve quality of life.

### **Diabetes**

An increased prevalence of impaired glucose tolerance and Diabetes mellitus has been observed in persons with schizophrenia. Overall, published findings from case reports, chart reviews, database analyses, and clinical trials demonstrate differing metabolic effects with the various first-generation antipsychotic (FGA) and SGA medications. Evidence is strongest for clozapine and olanzapine, with findings from published reports, including controlled experimental studies and randomized clinical trials, indicating that olanzapine and clozapine are associated with an increased risk of diabetes. The FDA's database of adverse events associated with haloperidol or second-generation antipsychotic drugs (in which the spectrum of diabetes-mellitus-related events Ranged from new-onset hyperglycaemia to life-threatening ketoacidosis has been analysed to estimate the strength of the association between a drug and diabetes- mellitus related adverse events, relative to that for all drugs and events. The adjusted reporting ratios for diabetes- mellitus related adverse outcomes were: olanzapine 9.6, 95% CI 9.2–10.0; risperidone 3.8, 95% CI 3.5–4.1; quetiapine 3.5, 95% CI 3.2–3.9; clozapine 3.1, 95% CI 2.9–3.3; ziprasidone 2.4, 95% CI 2.0–2.9; aripiprazole 2.4, 95% CI 1.9–2.9; and Haloperidol 2.0, 95% CI 1.7–2.3 (3). Diabetic ketoacidosis is often the first sign of antipsychotic drug associated diabetes mellitus among patients. Diabetic ketoacidosis is an acute complication of diabetes that mainly occurs in patients with type 1 diabetes,

but it is not uncommon in patients with type 2 diabetes. This condition is a complex disordered metabolic state characterized by hyperglycemia, ketoacidosis, and ketonuria. The mechanisms that cause weight gain by antipsychotics indirectly leads to diabetes in patients. Furthermore, Several cases of new-onset diabetes attributed to clozapine and olanzapine were associated with acute pancreatitis . It is possible, therefore, that antipsychotic-induced diabetes results from chemical damage to the pancreas. However, diabetes associated with atypical antipsychotics is associated with hyperinsulinemia rather than failure of insulin release. Antipsychotics also inhibit glucose transport into PC12 cells in culture and increase cellular levels of the glucose transporter isoforms GLUT1 and GLUT3. This scenario would lead to hyperglycemia, which in turn would cause a homeostatic increase in insulin release. Prolonged hyperinsulinemia could eventually lead to insulin resistance and further hyperglycaemia as a result of down regulation of insulin receptors. In most reported cases of hyperglycemia or diabetes associated with antipsychotics, the antipsychotic (usually clozapine or olanzapine) was either stopped completely or substituted with another antipsychotic. Although sometimes oral hypoglycemic agents or insulin were used. Lifestyle modifications to reduce blood glucose level is also implemented as a management strategy and periodic monitoring of blood glucose level is necessary.

### **Dyslipidemia**

Both first- (typical) and second-generation (atypical) antipsychotic drugs induce lipid abnormalities. The most commonly observed abnormality is an increase of 20 to 50 percent in triglycerides (TG), which is unsurprising given these drugs also are associated with weight gain and elevated glucose levels. A decrease in high-density lipoprotein cholesterol (HDL-C) and

increase in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) also have been observed, but these lipoprotein changes tend to be minor in comparison to the increases in TG. High-potency conventional antipsychotics (e.g., haloperidol) and the atypical antipsychotics, ziprasidone, risperidone and aripiprazole, appear to be associated with lower risk of hyperlipidemia. Low-potency conventional antipsychotics (e.g., chlorpromazine, thioridazine) and the atypical antipsychotics, quetiapine, olanzapine and clozapine, are associated with higher risk of hyperlipidemia. There are several proposed mechanisms that may explain how antipsychotics increase TG levels, including enhanced TG metabolism by stimulating hepatic production or inhibiting lipoprotein lipase-mediated TG hydrolysis, or indirectly via weight gain and obesity. The weight gain observed in patients receiving antipsychotics is primarily driven by appetite stimulation due to the effects these medications have on important serotonergic, dopaminergic, and histaminergic neurotransmitters. Additionally, the sterol-regulatory element-binding proteins (SREBPs), which affect lipid biosynthesis, also plays a major role in increasing TG. SREBP-1 regulates fatty acid and TG metabolism, while SREBP-2 regulates cholesterol metabolism. Antipsychotics increase SREBP activity, which may explain the observed increases in TG and cholesterol levels. Lipid profiles (that is, triglycerides and total, HDL and LDL cholesterol) should also be assessed at base line, As well as 6 weeks and 3 months after initiation of antipsychotic treatment, with annual assessments there after. If lifestyle measures are insufficient to correct dyslipidemia, treatment with lipid-lowering agents, such as statins, has been effective in patients taking antipsychotic drugs. Antipsychotic switching, antipsychotic add-ons are also used when necessary. Metformin (including both immediate-release and extended-



release formulations), and a combination of metformin–sibutramine seemed to have beneficial effects on lipid levels.

### **Orthostatic hypotension**

Orthostatic hypotension is the most frequent vascular effect of antipsychotic drugs, reported in up to 40% of patients (Mackin, 2008) and more commonly in elderly patients where the risk of damage from falling is greater. It is defined as a decrease in systolic blood pressure (SBP) of  $\geq 20$  mm Hg or diastolic blood pressure (DBP) of  $\geq 10$  mm Hg within 3 min of standing. It is more prevalent in combination of antipsychotics. Clozapine, olanzapine, quetiapine and risperidone have all been associated with changes in blood pressure related to posture (FDA, 1999, 2001a, 2001b, 2001c). 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. The complications of orthostatic hypotension include dizziness and visual disturbances, cognitive impairment, syncope, transient ischemic attack, stroke, myocardial infarction. The most accepted mechanism for antipsychotic related hypotension is  $\alpha 1$ -adrenergic blockade. Several other putative mechanisms such as calcium blockade, inhibition of centrally mediated pressor reflexes, and negative inotropic effects, have also been proposed for this adverse effect. Non pharmacological strategies and patient education, most notably, slowly rising from the supine position, are crucial first steps in the prevention and treatment of both symptomatic and asymptomatic orthostatic hypotension. Pharmacological treatment is only recommended when symptomatic orthostatic hypotension persists despite proper non pharmacological therapy and there is a compelling indication for antipsychotic treatment. Fludrocortisone is a

reasonable first choice for symptomatic orthostatic hypotension. Other agents including desmopressin and midodrine may be considered in patients who do not respond favourably to a trial of fludrocortisone.

### **CARDIOVASCULAR EFFECTS OF ANTIPSYCHOTICS**

There is great concern over cardiovascular disease in the schizophrenic population owing to the high incidence of cardiovascular mortality. Increased cardiovascular mortality is related to lifestyle choices (e.g., smoking and sedentary lifestyle) and a high prevalence of comorbid medical conditions, including dyslipidemia, the metabolic syndrome and Type 2 diabetes. One factor that increases cardiovascular risk is the medications used to treat the core features of schizophrenia. Adverse cardiovascular effects of antipsychotic treatment have been recognized for many decades, especially tachycardia, orthostatic hypotension and rare instances of sudden death. Antipsychotic drugs have been shown to produce either no change or an increase in heart rate (HR). As tachycardia is present in both supine and upright positions, it is not a reflex response to orthostatic hypotension. Tachycardia to antipsychotic treatment may be mediated via blockade of cardiac muscarinic M2 cholinergic receptors. Clozapine, the antipsychotic drug with the highest affinity for Muscarinic M2 relative to dopamine D2 receptors, appears to produce the most pronounced increase in HR. Some antipsychotics, such as clozapine and chlorpromazine, can block presynaptic  $\alpha 2$ -adrenoceptors, thus may increase sympathetic activity and indirectly activate the  $\beta$ -adrenoceptors in the heart to elevate HR. Heart rate variability is reduced in patients treated with some antipsychotic drugs. It is postulated that reduced heart rate variability by antipsychotic drugs is due to autonomic imbalance in the heart, as evident by augmented sympathetic and diminished vagal tone following clozapine treatment. The number of



drugs including antipsychotics like haloperidol, clomipramine, sertindole are associated with QT 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). As QT intervals normally shorten with increasing heart rate, and lengthen with decreasing heart rate, a rate corrected QT (QTc) Interval is often calculated. QT prolongation increases the likelihood of developing ventricular arrhythmias such as torsade De pointes, especially in susceptible individuals. Impaired autonomic function may contribute to antipsychotic induced cardiovascular abnormalities, especially in the development of arrhythmias. It has been shown that antipsychotic treatment decreases heart rate variability as a result of autonomic imbalance. Sympathetic hyperactivity has been implicated in the generation of arrhythmias and prolonged QT interval. The most common mechanism underlying QT prolongation appears to be blockade of the delayed rectifier potassium channel (IKR) 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 IKR blockade. 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. Myocarditis and cardiomyopathy have most consistently been linked with clozapine treatment. It is possible that non-fulminant, even subclinical, clozapine-induced myocarditis may progress to dilated cardiomyopathy, A condition characterised by cardiac dysfunction and often symptoms of congestive cardiac failure. Cardiomyopathy is

itself associated with a significant morbidity and mortality. It has been argued that clozapine-induced myocarditis results from a type 1 IgE-mediated hypersensitivity reaction. 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. A large pharmacoepidemiological study in patients receiving antipsychotic monotherapy (44,218 users of first-generation drugs, 46,089 users of second-generation and 186,600 nonusers matched for cardiovascular disease risk based on patient data on file), showed a similar, dose-dependent increase in the risk of sudden cardiac death (SCD) for patients treated with either first-generation or second-generation agents. The adjusted incidence rate ratios for SCD were similar for both typical and atypical anti psychotic drugs: 1.31 (95% CI 0.97–1.77) versus 1.59 (95% CI 1.03–2.46) for low doses (equivalent to <100 mg of chlorpromazine), 2.01 (95% CI 1.62–2.50) versus 2.13 (95% CI 1.70–2.65) for moderate doses (equivalent to 100–299 mg of chlorpromazine), and 2.42 (95% CI 1.91–3.06) versus 2.86 (95% CI 2.25–3.65) for high doses (equivalent to  $\geq 300$  mg of chlorpromazine).(24) Moreover, SCD is over-reported in mentally ill patients, who often have undiagnosed and untreated ischemic heart disease (which is by far the largest contributor to cardiac mortality).In addition, high doses of antipsychotic drugs are usually given to patients with more severe mental illness who have worse somatic health. Nevertheless, the excess of SCDs associated with anti psychotic use might be related to the effect of these drugs on myocardial repolarization, which is evident through their



varying, But well-established, propensity to prolong the corrected QT (QTc) interval. Whenever possible, every patient should undergo electrocardiography before the initiation of antipsychotic treatment.<sup>112</sup> Baseline electrocardiography is especially important, and should be mandatory, in patients with risk factors for QTc prolongation, cardiac arrhythmias or SCD. For patients with a high risk of SCD, such as those with diabetes mellitus or the metabolic syndrome, annual electrocardiography should be considered.

## CONCLUSION

Second-generation antipsychotic agents offer similar efficacy to first-generation agents, but are associated with fewer extrapyramidal symptoms and reduced risks of treatment discontinuation and relapse. However, concerns about extrapyramidal symptoms have been replaced by those about cardiovascular and metabolic adverse effects, such as obesity, impaired glucose tolerance, diabetes mellitus and dyslipidemia. In particular, obesity can have a important negative impact on patient's overall health in relation to changes in insulin sensitivity and the associated risk of hypertension, hyperglycemia, and hyperlipidemia—all additional cardiometabolic risk factors. The affinity of anti psychotic drugs for the histamine H1 receptor is most closely linked to increased weight gain, although their affinity for dopamine D2 and serotonin 5-HT<sub>2c</sub> receptors might also be involved. An affinity specifically for the muscarinic M3 receptor correlates with an increased risk of diabetes mellitus. Based on substantial evidence that some treatments can increase adiposity, alter plasma lipids, and increase the risk of hyperglycemia, clinicians must be alert for potential negative effects on cardiometabolic risk. Clinicians should monitor and appropriately treat cardiometabolic risk in patients. Alterations in the autonomic nervous system may play a role in antipsychotic-induced cardiovascular effects. Some of these changes may

involve blockade of peripheral adrenergic and cholinergic receptors, as well as increase in sympathetic activity. The second-generation drugs ranked from high to low in terms of cardiovascular and metabolic adverse effects are as follows: clozapine = olanzapine, > quetiapine, ≥risperidone = paliperidone, >amisulpride, ≥ aripiprazole, ≥ziprasidone. Of the first-generation agents, the low potency agents have the highest, and the high-potency agents have the lowest, potential to cause cardiovascular and metabolic dysfunction. Baseline and follow-up assessment of cardiovascular and metabolic abnormalities in patients treated with second-generation antipsychotic drugs is currently insufficient. Clearly, lifestyle-related factors that are easy to measure, such as weight, waist circumference and blood pressure, should be monitored at appropriate intervals in all patients treated with antipsychotic drugs. In addition, psychiatrists, physicians, nurses and other members of the multidisciplinary care team can educate and motivate people with severe mental illness to improve their lifestyle through effective behavioural interventions, including smoking cessation, dietary measures and regular exercise. However, if lifestyle interventions do not succeed, other medications, including statins, antihypertensive therapy or antidiabetic agents, might be indicated.

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