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Review Article
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Cardiometabolic effects of psychotropic medications

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Abstract:
Background: Many psychiatric disorders including schizophrenia, bipolar disorder and major depression convey an excess burden of cardiovascular morbidity and mortality. The medications used to treat these conditions may further adversely affect cardiovascular risk and exacerbate health disparities for vulnerable populations. There is a clinical need to appreciate the cardiometabolic adverse effects of psychotropic medications.

Methods: This paper reviews the most relevant cardiometabolic effects of psychotropic medications, organized around the components of metabolic syndrome. When known, the molecular and physiological mechanisms underlying any adverse cardiometabolic effects are detailed.

Results: Many commonly used psychotropic medications, particularly antipsychotics, mood stabilizers and some antidepressants, have been independently associated with cardiometabolic risk factors such as insulin resistance, obesity and dyslipidemia. Stimulants, antidepressants that inhibit reuptake of norepinephrine, some antipsychotics and valproic acid derivatives may also increase blood pressure.

Conclusion: Understanding, assessing and subsequently managing cardiometabolic complications of psychotropic medications is important to mitigate the excess cardiovascular morbidity and mortality in the clinical populations prescribed psychotropic medications. There is considerable variability in risk between medications and individuals. Timely management of iatrogenic cardiometabolic effects is critical.

Keywords: adverse effects, anticonvulsants, antidepressive agents, antipsychotics, diabetes mellitus, dyslipidemias, lithium, metabolic syndrome, psychotropic drugs, weight gain

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Introduction

Metabolic syndrome also known as syndrome X or insulin-resistance syndrome is a cluster of conditions that occur together with insulin resistance as a common feature. The components of the syndrome include hypertension, central obesity, dyslipidemia [high triglycerides and low high density lipoprotein cholesterol (HDL-c)] and impaired glucose tolerance [1]. Many commonly used psychotropic medications adversely impact these components of metabolic syndrome as illustrated in Figure 1. These individual components of metabolic syndrome, which are risk factors for vascular disease, are the focus of this review.

Figure 1: Summary of psychotropic medications associated with cardiometabolic iatrogenic effects.

This figure summarizes the medications or medication classes, where appropriate, associated with the cardiometabolic adverse effects that served as the focus of this review: weight gain, dyslipidemia, insulin resistance or frank type 2 diabetes mellitus and hypertension.

Three broad classes of medications with the potential for cardiometabolic side effects are commonly used in the management of many psychiatric conditions: antidepressants, mood stabilizers and antipsychotics. Antidepressants are a mainstay in the treatment of anxiety and depressive disorders. While antidepressants may be combined with other agents, like fluoxetine (antidepressant) and olanzapine (antipsychotic) for bipolar depression [2], this review will focus on individual medications rather than combination products. Mood stabilizers include lithium, valproate (divalproex), carbamazepine and lamotrigine, many of which have anticonvulsant properties. These are the foundation for the treatment of bipolar disorder and are sometimes used in other mood disorders. Antipsychotics are another important class, commonly divided into the first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). Well-known FGAs include: fluphenazine, haloperidol and chlorpromazine. SGAs include agents such as aripiprazole, olanzapine, clozapine, quetiapine and risperidone. SGAs have become popular for treatment of more than just psychotic disorders and are even used off label for treatment of conditions such as insomnia, but these agents are associated with substantial risk of metabolic complications [3], [4], [5], [6], [7], [8]. Medication selection is dependent on several factors including, but not limited to, targeting acute psychiatric syndromes and the prevention of future episodes. Medication selection should also be driven by consideration of side-effects and there is evidence to suggest that physicians, particularly psychiatrists, underappreciate cardiometabolic adverse effects when prescribing psychotropic medications [9].

Weight gain

Large weight gains on the order of 3–5 kg/m² over 2 years in those with a body mass index (BMI) ≥ 35 are associated with a 33%–53% increase in mortality independent of risk factors [10]. The clinical significance of gains in individuals in those within the normal weight range is less clear. Many psychiatric disorders are associated with weight gain after the onset of illness and institution of medication. A systematic review demonstrated increase in body weight by 10%–12% in the first 6–12 months following diagnosis and treatment of schizophrenia [11]. In a separate study, among 128 depressed patients prescribed imipramine over 33 weeks, 13% demonstrated increased weight of more than 10% over 5 months [12]. Most of the weight gain occurs in the first 6 months and is more prominent if the patient is already overweight [13], [14]. Some of the predictors for weight gain include young age, female gender, low BMI and family history of obesity, the dose and duration of treatment [15]. A
long-term retrospective analysis (mean of 7 years) has clarified that a low BMI predicts higher acceleration of BMI change, but that a high premorbid BMI is associated with a greater total change in BMI [15]. Parents BMI is also predictive [15]. A strong predictor for long-term weight gain with antipsychotics is at least a 5% weight gain from baseline within the first month of treatment [16]. Therefore, the changes in weight for each patient must be monitored rigorously as they can have a great impact on the quality of life and importantly, early changes in treatment can prevent severe adverse effects [17]. There is substantial variability in weight gain across patients taking psychotropic medications. A 3-month study of 135 antipsychotic-naive children on risperidone demonstrated varied weight changes from weight loss in 4.4% of the cohort to weight gains of greater than 21% in 6.7% patients (Figure 2) [18]. This emphasizes the need for ongoing monitoring and assessment.

![Figure 2: Variability in observed weight gain.](image)

This figure illustrates the considerable individual variability in weight changes that can be seen with antipsychotic treatment. These data were from a Correll et al. [18] study of 135 antipsychotic-naïve children and adolescents treated with risperidone for 3 months. The mean weight gain in this study was 5.3 kg. Antipsychotic-naïve individuals gain more weight than those with prior treatment.

**Antipsychotics**

Antipsychotic medications commonly cause weight gain. Increased weight has been reported in 40%–80% of individuals on FGAs and SGAs [11]. Clozapine, olanzapine, and quetiapine, risperidone are most likely to produce severe weight gain. Comparison of five antipsychotic medications in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), a publicly-funded comparative effectiveness study demonstrates relative differences in weight gain between the five antipsychotic agents studied (Figure 3) [19]. Over a quarter (28%) of the participants reported antipsychotic use at baseline. The olanzapine group demonstrated the greatest weight gain with participants randomized to olanzapine gaining an average of 2 lb (0.9 kg) per month above their baseline weight [19]. The effect of antipsychotics on weight has been compared most commonly to the effect that lithium has on weight. There was a greater than 15% weight gain more often in people prescribed olanzapine (HR = 1.84; p < 0.0001) or quetiapine (HR = 1.67; p < 0.001) compared to lithium [20]. Patients randomized to quetiapine for acute mania gained 3.3 kg in a 12-week efficacy clinical trial for acute mania vs. 1.0 kg on lithium [21]. In a separate meta-analysis comparing the effects of different antipsychotics on weight, the smallest weight gains were associated with ziprasidone, fluphenazine and haloperidol, [22] while molindone was actually associated with weight loss [23]. Aripiprazole is sometimes considered weight neutral, occasionally causing weight loss with acute use [24] or weight gain especially in the young [25]. However, even with aripiprazole, 8%–11% of patients may gain >7% of baseline weight after just 4 weeks of treatment [26]. All antipsychotics should be considered to carry the potential for extreme weight gain in vulnerable individuals [9]. Reviews of randomized placebo-controlled trials highlight the importance of individual variability and underscore the importance of ongoing monitoring [18]. The variability of reported changes in weight with antipsychotic medications is substantial. Rummel-Kluge and colleagues conducted a meta-analysis of randomized control trials contrasting weight gain across SGAs. There was heterogeneity in the degree of weight changes observed among studies with differences due to dosage of medication prescribed, duration of treatment and age of the samples, which across studies averaged in their mid-30s [27]. In head-to-head comparisons, clozapine produced significantly more weight gain (mean difference 2.9 kg) than risperidone. Olanzapine resulted in significantly more weight gain than amisulpride (2.1 kg), aripiprazole (3.9 kg), quetiapine (2.7 kg), and risperidone (2.4 kg) and ziprasidone (3.8 kg). Risperidone also yielded more weight gain than amisulpride (1.0 kg) while sertindole caused more weight gain than risperidone (1.0 kg) [27].
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Figure 3: Weight gain for antipsychotics used in the CATIE study.

The CATIE study randomly assigned 1493 patients with schizophrenia to flexibly dosed olanzapine (7.5–30 mg/day), quetiapine (200–800 mg/day), risperidone (1.5–6.0 mg/day), perphenazine (8–32 mg/day) and, introduced in the latter portion of the study, ziprasidone (40–60 mg/day). The greatest weight gain was observed with olanzapine, followed by quetiapine and risperidone [19], where 1 pound (lb) equals approximately 0.45 kg.

Mood stabilizers

Two of the more common mood stabilizers prescribed are valproate (divalproex) and lithium and both have been associated with weight gain. A 12-week randomized clinical trial by Bowden and colleagues [28] demonstrated significantly more weight gain with valproate than with lithium (1.1 vs. 0.2 kg; \( p = 0.04 \)). Although, patients on valproate gained more weight than those on lithium, this did not appear to be as clearly dose dependent with valproate as with lithium [29]. Lithium-associated weight increases are less likely at plasma levels <0.8 mmol/L [30]. It is nonetheless not uncommon to observe a 4-kg weight gain during the first 2 years of treatment with lithium. Alternatively, other mood stabilizers such as lamotrigine or carbamazepine appear to have little effect on weight [31], [32]. Nonetheless, 11% of 173 subjects treated with lamotrigine, in a double blind phase of a randomized control trial, had weight gains of greater than 7% [31]. Most of the fat distribution seen with psychotropic drugs is located around the abdomen with a higher waist-to-hip ratio in patients taking valproate than in lean patients (\( p < 0.001 \)) [33], associated with the metabolic syndrome.

Antidepressants

With antidepressants, weight gain may be due to improvements in depressive symptoms (i.e., resolution of decreased appetite) following treatment, or side-effect of antidepressants that presents as weight gain persisting after symptom remission [34]. Substantial weight gains have been reported for amitriptyline, mirtazapine and nortriptyline. In a meta-analysis of weight changes with antidepressants, weight gain of 1.52 kg was seen with amitriptyline, 1.74 kg with mirtazapine and 2.00 kg with nortriptyline over a 4–12-week period, while other non-tricyclic antidepressants were not associated with weight gain [35]. With medium- and long-term treatment, however, more antidepressants are associated with weight gain of more than 1 kg: paroxetine 2.73 kg, mirtazapine 2.59 kg, amitriptyline 2.24 kg, citalopram 1.69 kg and nortriptyline 1.24 kg. In the Netherlands Study of Depression and Anxiety comparing long-term side effects of all the antidepressants, the prevalence of self-reported weight gain was highest with mirtazapine (29%), followed by tricyclic antidepressants (TCAs) (22%) and selective serotonin reuptake inhibitors (SSRIs) (19%) after 1-year of follow-up [36]. Other antidepressant agents such as escitalopram, imipramine, fluvoxamine and trazodone showed no significant weight changes. Treatment with paroxetine, sertraline and fluoxetine resulted in mean changes in weight of 3.6%, 1% and −0.2%, respectively, at the end of 26–32 weeks. Extreme weight gain (>7%) was more prevalent in patients taking paroxetine (25.5%) than those taking sertraline (4.2%) or fluoxetine (6.8%). Risk for greatest weight gain was seen in those with a lower baseline BMI (short-term weight gain) and a family history of obesity [34]. A long-term follow-up of claims data did not show substantive differences between SSRIs in risk of weight gain with a pattern for no changes in weight in the first 3 months followed by steady increases in weight between 3 and 12 months [37]. Unlike other antidepressants, weight loss has been observed with bupropion [35], which tends to be proportional to the baseline BMI with only minimal decreases in weight observed amongst those who are underweight of normal weight [38].

A lack of head-to-head comparisons between psychotropic medications and heterogeneity in study design and clinical samples (e.g., treatment-naïve vs. those later in course of illness and treatment), renders it difficult to make precise determinations regarding relative liabilities for weight gain across medications. As already mentioned, there is also considerable variability in individual vulnerabilities in these adverse events. Figure 4
illustrates approximate propensity for weight gain of the agents discussed, although caution should be exercised in ascribing relative differences for any agents not assessed head-to-head in a randomized clinical trial.

Figure 4: Propensity for weight gain for selected psychotropic medications.

Mechanisms of weight gain

A variety of mechanisms may explain the weight gain caused by psychotropic medications. Many psychotropic medications antagonize histamine-1 receptor (H₁) [39], serotonin (5-HT₂₅, 5-HT₂C) [40] and α₁-adrenergic receptors [41]. The affinity of antipsychotics for these receptors correlates highly with weight gain [42]. Antagonism of serotonin and histamine receptors leads to increased central appetite and thus increased food intake. Additionally, H₁ blockade increases carbohydrate craving and intake [41]. Monoamine oxidase inhibitors (MAOIs) and TCAs are thought to induce a greater weight gain than other antidepressants due to more potent H₁ receptor antagonism [43]. SSRIs cause an initial reduction in 5-HT₂C receptors promoting subsequent stimulation of presynaptic 5-HT₁ receptors [44]. Fluoxetine has a high attraction for 5-HT₂C receptors and antagonizes these receptors leading to increased appetite, yet it is associated with weight loss acutely. In a prospective study, 832 patients on fluoxetine, treated over 50 weeks were observed to experience a weight loss of <0.5 kg during the open-label acute non-randomized phase (4 weeks) whereas the double-blind randomized continuation phase (week 12–week 50) was associated with steady weight increases by 1.1 kg (at week 26), 2.2 kg (at week 38) and 3.1 kg (at week 50), respectively [45]. The reason for the differences between short-term and long-term weight effects with fluoxetine or other SSRIs has not been convincingly explained [46].

Conversely, weight loss is associated with bupropion [47], [48], [49]. Blocking dopamine and norepinephrine reuptake, as bupropion does, has been associated with weight loss. Bupropion has no effect on adrenergic, histamine or serotonergic receptors [50]. Comparisons between sertraline and bupropion in binge eating disorder showed no weight loss in the first 6 weeks but by week 14, 60% of those on bupropion had lost 5% of their weight [51]. Similarly, in a randomized, placebo-controlled trial by Croft and colleagues [38] involving 828 patients over 44 weeks, weight loss with bupropion was proportional to baseline BMI and this weight loss was dose dependent.

Psychotropic medications may adversely influence weight by interfering with the regulation of leptin and adiponectin. Leptin is a hormone responsible for controlling body weight through phosphorylation of protein kinase B (PKB). PKB in the presence of psychotropic medications such as lithium acts through a negative feedback to inhibit glycogen-synthase-kinase 3 beta (GSK3β), which blocks the ability of leptin to reduce food intake resulting in weight gain [52]. This same effect is seen with valproate. A systematic review of valproate-induced insulin resistance could not find compelling evidence to suggest hyperinsulinemia or hyperleptinemia is due to anything other than obesity, with more research needed to understand the mechanisms [53].

Adiponectin is an adipocyte-derived protein; its main role is to regulate insulin sensitivity and glucose homeostasis. Animal studies with mice and in vitro studies using mature adipocytes by Qiao et al. examined the effect of valproate on adiponectin gene expression. Valproate had a dose-dependent inhibitory effect on the gene expression of adiponectin in both mature fat cells and mice, this effect is also time dependent. By inhibiting an essential enzyme in deoxyribonucleic acid (DNA) transcriptional regulation, histone deacetylase, other essential
enzymes are repressed leading to decreased adiponectin expression and obesity-associated insulin resistance [54].

An alternative explanation for weight gain by psychotropic medication involves the insulin-like effect of medications such as lithium. In a study on rats, following treatment with lithium, glucose administration was followed by decreased insulin levels and higher blood glucose levels [55]. Rose and Warms noted glucose 1,6-P2 synthase activity was lower in animals treated with lithium because lithium replaces zinc as an enzyme activator. This ultimately results in an insulin-like effect thus causing glucose tolerance [56]. The proposed mechanism involves cyclic adenosine monophosphate (cAMP) inhibition in the pancreas, leading to inhibition of insulin secretion and antagonism of sodium and calcium ions by lithium, which are responsible for insulin secretion [57].

**Dyslipidemia**

Dyslipidemia is another major adverse metabolic outcome associated with psychotropic medications and appears strongly related to medication-induced weight changes. Higher cholesterol levels are associated with substantially increased risk of cardiovascular mortality. The Multiple Risk Factor Intervention Trial (MRFIT) was a prospective trial that looked at mortality risks among young men over a 16-year follow-up period. The study found a two- to four-fold increased risk of deaths due to coronary heart disease in men with high cholesterol levels (>240 mg/dL (6.21 mmol/L)) compared to those with low cholesterol levels (<200 mg/dL (<5.17 mmol/L)) [58]. Additionally, men with better cholesterol levels (<200 mg/dL) had a greater life expectancy of 3.8–8.7 years compared to men with higher cholesterol levels [58]. Any low density lipoprotein cholesterol (LDL-c) level above 100 mg/dL is considered atherogenic and can increase the risk of cardiovascular disease [59].

**Antipsychotics**

The antipsychotics clozapine and olanzapine have been highlighted in several studies as being particularly predisposing to metabolic adverse effects [23], [60]. Olanzapine and clozapine are well known to cause significant hyperlipidemia and hypertriglyceridemia [61]. A Veterans’ Affairs analysis demonstrated the greater risk of dyslipidemia following treatment with olanzapine or quetiapine than with risperidone or haloperidol [61]. Hypertriglyceridemia with antipsychotics can be remarkably rapid; triglyceride levels may double as soon as in 2 weeks with risperidone use [62]. The magnitude of changes with most antipsychotics is equally substantial, especially in triglyceride levels. Overall, most common antipsychotics prescribed increase risk for lipid abnormalities in varying degree clozapine [odds ratio (OR) = 1.82, 95% confidence interval (CI) 1.61–2.05], olanzapine (OR = 1.56, 95% CI 1.47–1.67), FGAs (OR = 1.26, 95% CI 1.14–1.39) and aripiprazole (OR = 1.19, 95% CI 0.94–1.52) [61].

**Mood stabilizers**

Mood stabilizers are also associated with hyperlipidemia. Fifty-three children receiving carbamazepine, phenobarbital and valproic acid over a 12-month period had initial assessments that demonstrated a non-statistically significant increase in total cholesterol, HDL-c, LDL-c and triglycerides for all three agents which were persistent up to 1 year later [63]. Significant weight gain places additional risk for dyslipidemia. Lithium is not directly associated with dyslipidemia, [64] but its effects on lipids may occur secondary to lithium-induced hypothyroidism, which adversely impacts weight and lipids [65]. Several studies have shown an increase in triglyceride level in patients treated with valproate; however, no significant change in cholesterol levels were found [66], [67], [68]. Interestingly, there are reported reductions in total and LDL cholesterol in patients with schizophrenia and bipolar disorder treated with mood stabilizers [69], [70] despite increased triglycerides, weight gain and glucose and insulin abnormalities [71].

**Antidepressants**

Few studies and case reports are available to support the changes in lipid synthesis and storage with antidepressant use. Teitelbaum reported the case of a 46-year-old male with depression who had baseline triglyceride levels of 490 mg/dL. Following an initial treatment with fluoxetine for 3 years, he was switched to citalo-
pram due to fluoxetine-induced side effects. Subsequently, his triglyceride levels increased to 846 mg/dL in a span of 3 months. Withdrawal of citalopram returned triglyceride to lower levels (223 mg/dL) [72]. In a small-randomized controlled trial, mirtazapine significantly increased cholesterol over 4 weeks compared to placebo (+7.6 mg/dL vs. −0.04 mg/dL) [73]. SSRI use has been cross-sectionally associated with hypercholesterolemia (OR = 1.36, p = 0.012) but not hypertriglyceridemia [74]. A case-control study conducted by Melledo and colleagues [75] showed an 11.5% statistically significant increase in mean LDL-c with paroxetine administered to both healthy adults and individuals suffering from panic disorder after 8 weeks of treatment.

Mechanisms of dyslipidemia

Although, the exact mechanism for changes in lipid profile following treatment is unknown; several plausible pathways have been proposed. Lipid abnormalities may follow observable weight gain associated with prescribed medications, increased lipid biosynthesis through induced gene expression of specific enzymes necessary for lipid metabolism [67] or altered lipid metabolism through different pathways. These pathways may include incorporation of 14 C-acetate into fatty acids and derived lipids, or enzyme inhibition and induction in cholesterol synthesis or through the synthesis of apolipoprotein B [76]. FGAs and SGAs are amphiphilic and act on cholesterol biosynthesis at the cellular level. Haloperidol inhibits the cholesterol biosynthetic reaction catalyzed by Δ-7 reductase, Δ-8, 7 isomerase and Δ-14 reductase. Clozapine inhibits Δ-24 reductase and/or Δ-8,7 isomerase reactions. Risperidone inhibits Δ-7 reductase, Δ-14 reductase and 14-α-demethylase, while ziprasidone inhibits Δ-7 and Δ-14 reductase [76]. This results in accumulation of different sterol intermediates in the cholesterol biosynthesis pathway leading to increased synthesis of complex lipids (phospholipids and triglycerides) [77]. Antidepressants activate sterol regulatory element-binding protein (SREBP) transcription factors, subsequently upregulating genes which are responsible for cholesterol and fatty acid biosynthesis [77]. TCAs such as clomipramine, imipramine and amitriptyline are the most potent activators of SREBP. Citalopram and mirtazapine activate it to a lesser extent, with fluoxetine and bupropion activating it only marginally. Mood stabilizers were not found to activate SREBP. Antiepileptic medications like carbamazepine and phenytoin are potent cytochrome P450 system (CYP450) inducers [78]. These medications induce CYP51A1, an enzyme responsible for catalyzing conversion of the precursor lanosterol to cholesterol in the latter part of the cholesterol synthetic pathway. The substrates on which it acts provide negative feedback inhibition on hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme for the pathway. Induction of this enzyme leads to increased conversion to cholesterol and loss of feedback inhibition on HMG-CoA reductase, which increases cholesterol production. Mintzer and colleagues [79] demonstrated statistically significant improvements in triglycerides (~47.1 mg/dL), total cholesterol (~24.8 mg/dL) and LDL-c (~19.9 mg/dL) after switching patients who were on carbamazepine or phenytoin (inducers) to levetiracetam or lamotrigine (non-inducing anti-epileptic medications) concluding that anti-convulsant medications may increase cardiovascular morbidity risk through effects on lipids.

Insulin resistance and the development of diabetes mellitus

Strong links exist between psychotropic medications and the development of insulin resistance, worsening of insulin resistance and development of overt diabetes [80], [81]. Data from the National Health and Nutrition Examination Survey (NHANES) demonstrate a 2.5 greater prevalence of diabetes in an age-matched sample taking antipsychotics and valproic derivatives than in the general population [80], [82].

Antipsychotics

While SGAs were promoted for having lower risk of extrapyramidal side effects and tardive dyskinesia than FGAs, evidence of worsening blood glucose with resolution of symptoms following withdrawal of SGAs was identified [83], [84]. Adolescents taking SGAs were found to have a 50% increased occurrence of type 2 diabetes mellitus relative to those not taking SGAs [85]. A retrospective cohort analysis of 484 patients on FGAs (haloperidol, fluphenazine, chlorpromazine and perphenazine) and olanzapine revealed a high plasma glucose level (>160 mg/dL) in 10.5% of patients on olanzapine, as compared to normal glucose levels in patients on FGAs [86]. Nonetheless, a retrospective study of 7139 subjects with schizophrenia from the Danish Central Psychiatric Research Registry suggests that initial treatment with mid-potency FGAs (zuclopenthixol, perphenazine) and current treatment with low-potency FGAs (chlorpromazine, levomepromazine) could lead to diabetes. SGAs tested in this cohort (olanzapine, OR: 1.44, CI 1.98–1.91) undoubtedly seem to be a risk factor
for insulin resistance and diabetes mellitus and thus research has focused on their potential mechanisms [87].

The risk for development of diabetes in those taking risperidone and quetiapine was lower than olanzapine [88], [89]. A systematic analysis using the United States Food and Drug Administration data demonstrated that aripiprazole and ziprasidone are less likely to cause diabetes-related adverse events as compared to olanzapine, clozapine, risperidone and quetiapine [90].

### Mood stabilizers

Valproic acid derivatives are another potential culprit for insulin resistance in those with bipolar disorder. A longitudinal cohort study in patients with epilepsy on valproate showed that increased insulin levels were found in the patient group who reported weight gain, possibly due to increased appetite [91]. In a systematic review of randomized trials that looked at various mood stabilizers, valproate users were at a greater risk of weight gain (RR = 2.04, p = 0.03), which could lead to insulin resistance [92]. Animal studies demonstrated no statistically significant differences in insulin levels between the lithium and placebo groups [93]. Lithium does exert an insulin-like effect on glucose transport in animal models. This has been a rationale for use of lithium to treat insulin resistance in non-insulin dependent diabetes mellitus [94], [95].

### Antidepressants

With antidepressant medication use, depressive mood symptoms were associated with abnormalities in glucose metabolism and elevated insulin levels in a case-control study with 20 depressed patients and 13 matched healthy controls [91]. Although some of the decreased insulin sensitivity may be illness and not medication related, recent studies suggested abnormalities in insulin function with antidepressant medications may be centrally mediated at the level of the hippocampus through neurohormonal effects on metabolism [96]. In a review of randomized control trials of antidepressant medications, McIntyre and colleagues concluded that serotonergic antidepressants in general lower blood glucose levels. A 24-week placebo-controlled study examined glucose levels in 48 obese patients with type 2 diabetes mellitus. In the fluoxetine randomized group, hemoglobin A₁c (HbA₁c) levels were significantly lower (9.72% vs. 10% 10.76, p < 0.005) [97]. Fluoxetine was the most widely studied medication, venlafaxine and duloxetine were found to be metabolically neutral. TCAs are the only group of antidepressants that are associated with increased blood glucose levels [96].

### Mechanisms for insulin resistance

Animal studies have elucidated many possible mechanisms on how insulin resistance may be induced by SGAs. Studies on rats have shown the SGA olanzapine increases serum glucose concentration in a dose-dependent manner. Olanzapine activates AMP-activated protein kinase (AMPK) in the hypothalamus, which causes hepatic gluconeogenesis via the sympathetic nervous system [98]. Another study on rats showed that olanzapine significantly increased saturated fatty acids and significantly decreased monounsaturated fatty acids in rat plasma. This change in the fatty acid profile may play a role in insulin resistance by unknown mechanisms. Olanzapine-induced hyperglycemia was prevented by the AMPK inhibitor compound C, providing further evidence that AMPK is involved [99]. Other evidence suggests the hyperglycemia is due to central insulin’s inability to suppress the hepatic glucose production [100]. Psychotropic medications may also predispose to insulin resistance through an epigenetic mechanism [101]. In humans, SGAs have been found to decrease global DNA methylation, and associations between SGA-induced insulin resistance and hypomethylation have been demonstrated [101]. A differentially methylated CpG site on the Fatty Acyl CoA Reductase 2 gene was associated with SGA-induced insulin resistance [102]. In aggregate, it appears that multiple pathways may be responsible for SGA-induced insulin resistance.

### Hypertension

A less studied vascular adverse effect associated with psychotropic medications is increased blood pressure. Incremental elevations in blood pressure over 115/75 mm Hg have been associated with a greater risk of cardiovascular mortality in both men and women [103]. The risk of cardiovascular death in both women and men doubles with each increase of 20 mm Hg systolic and 10 mm Hg diastolic blood pressure [103]. Hence, the potentially clinically significant effects on blood pressure of these medications on the blood pressure should be
kept in consideration when treating psychiatric conditions particularly in those who are also being managed for hypertension. A study by Goldstein and colleagues demonstrated higher blood pressures in individuals treated for bipolar disorder than healthy controls. Specific details regarding psychiatric medications prescribed was not obtained, precluding any differentiation by class [104]. In addition to efficacy trials of stimulants used in psychiatric managements [105], [106] animal models also demonstrate a dose-dependent statistical increase in blood pressure [107].

Orthostatic hypotension is a more common side effect of most psychiatric medications. As such, more reported evidence of orthostatic hypertension exists [108], [109]. However, in the spirit of the cardiometabolic focus of this review, this section highlights the cardiovascular impact of psychotropic medications through hypertension, which is a component of the metabolic syndrome.

**Psychostimulants**

Psychostimulants are well known to cause elevations in blood pressure. In a double-blind, randomized crossover trial of children with attention deficit hyperactivity disorder on methylphenidate, amphetamine or dextroamphetamine, diastolic blood pressure elevations of 3–4 mm Hg were observed on 24-h ambulatory blood monitoring [110]. Methylphenidate has been associated with similar elevations in blood pressure in adults, 3.5 mm Hg in systolic and 4.0 mm Hg in diastolic blood pressure, with considerable individual variability [111]. A smaller systolic blood pressure increase of 2.0 mm Hg has been reported for the norepinephrine reuptake inhibitor and stimulant alternative, atomoxetine [112].

**Antidepressants**

Increases in blood pressure have also been demonstrated in the use of antidepressants such as venlafaxine, duloxetine and TCAs, which inhibit norepinephrine reuptake [113]. Depression is generally associated with a lower blood pressure but antidepressant use is associated with increased blood pressure. A case control study from the Netherlands Study of Depression and Anxiety demonstrated that a person on antidepressant was 2 times more likely to have elevated blood pressure [114]. In a meta-analysis of several clinical studies including 3744 patients with depression, venlafaxine (1.2 mm Hg) and imipramine (1.0 mm Hg) had statistically significant increases in supine diastolic pressures relative to placebo (−1.5 mm Hg) [115].

**Antipsychotics**

In 2013, Yasui-Furukori and Fujii recorded two unique cases documenting a steep increase in blood pressure following treatment with aripiprazole causing blood pressure readings of 200/110 mm Hg and 180/90 mm Hg, which improved after the medication was discontinued. Both patients reported headache while taking the medication, a symptom frequently associated with hypertension [116]. Clozapine, olanzapine and ziprasidone have been associated with hypertension, while quetiapine and risperidone appear to have little effect on blood pressure [117], [118]. Animal models similarly showed increased weight and blood pressure in those given olanzapine [107].

**Mood stabilizers**

With mood stabilizers like lithium, animal models demonstrated antihypertensive effects [119] through its similar renal effects in humans [120]. Valproate, on the other hand, has been associated with hypertension in 1%–5% of patients, [121] including a case report of a valproate-associated hypertensive urgency in an 8-year-old child which resolved with discontinuation of the medication [122].

**Mechanisms of blood pressure elevation**

While most SGAs antagonize 5HT2A, aripiprazole is a 5HT2A receptor partial agonist. 5HT2A causes contractions in the smooth muscles of vasculature, which increases vessel resistance. Aripiprazole acts as an agonist on the 5-HT2A receptor resulting in hypertension. Additionally, a possible antagonism of α1 adrenergic receptors
by aripiprazole may be driving the changes observed in blood pressure [116], [123]. TCAs and FGAs have anticholinergic effects that may be responsible for increases in blood pressure [124]. Weight gain associated with antipsychotics or other psychotropic medications may also mediate changes in blood pressure. Individuals with obesity develop a selective resistance to the appetite suppression hormone, leptin. The hypothalamus becomes resistant to the anorexigenic effects of leptin, which ordinarily would decrease appetite and increase satiety. Resistance to leptin does not occur with regard to the regional sympathetic nerve activity response to leptin in the renal tissue and brown adipose and lumbar tissues [125]. The increased renal sympathetic nerve activity results in obesity-induced hypertension due to selective leptin resistance.

Blood pressure elevation is more directly mediated through the effects on neurotransmitters. Psychostimulants such as amphetamines directly release norepinephrine, dopamine and serotonin into synapses, which increase the blood pressure through central dopaminergic and peripheral adrenergic effects [126], [127]. Studies of the norepinephrine reuptake inhibitor atomoxetine in those with central and peripheral autonomic failure suggest blood pressure increases occur through selective norepinephrine transporter blockade in peripheral sympathetic neurons. These effects are attenuated by central sympatholytic mechanisms and subsequently exacerbated in those with central autonomic failure [128]. TCAs similarly increase norepinephrine through reuptake inhibition, which leads to an elevation of blood pressure. FGAs have anticholinergic effects, which may elevate blood pressure [114]. Presynaptic dopamine-2 receptors (D2) can inhibit sympathetic nerve activity and this may acutely influenced by antipsychotics [129], whereas, with carbamazepine, elevations in blood pressure may be following increase in antidiuretic hormone [130] or antagonism of central noradrenergic receptors [131], although the exact mechanism still remains uncertain. Similarly, valproate is known to act through increasing the circulating gamma-aminobutyric acid (GABA), blocking sodium channels and inhibiting glutamate/N-methyl-D-aspartate (NMDA) receptor-mediated neuronal excitation [132]. Carbamazepine works in an analogous manner, which in turn may be due to its similarities in structure to imipramine (an antidepressant) [133].

### Discussion

Several guidelines are available to help clinicians monitor side effects of commonly used psychotropic medications. The most prominent is the American Diabetic Association and American Psychiatric Association (ADA-APA) guidelines for monitoring the metabolic consequences of SGAs, which are summarized in Table 1 [83]. Two guidelines have suggested that HbA1c can be substituted for fasting glucose [134]. Where obtaining fasting labs might be a barrier, such as in patients who do not present to the clinic fasting and may not be reliable in obtaining a subsequent fasting lab draw, non-fasting lipids may be substituted [135].

<table>
<thead>
<tr>
<th>History of risk factors*</th>
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<tr>
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</tbody>
</table>

*Personal and family medical history of cardiovascular risk factors (obesity, hypertension, diabetes mellitus) or cardiovascular disease.

This table highlights the recommendations from a consensus statement published by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity. While these guidelines were drafted in response to mounting concerns about the adverse effects of second-generation antipsychotics, they provide a reasonable framework for the monitoring of other medications associated with similar cardiometabolic risk. The guidelines also recommend that patients, family and providers be aware of signs or symptoms of diabetes mellitus and diabetic ketoacidosis [83].

Despite available guidelines, studies have shown that recognition and treatment of the cardiometabolic adverse effects of psychotropic medications is inadequate [136], [137]. The ADA-APA guidelines also recommend...
selecting an agent with a lower propensity for weight gain and glucose intolerance in those with or at a higher risk of diabetes [83]. Unfortunately, clinicians, in general, do not appear to take preexisting diabetes mellitus, hyperlipidemia into consideration when selecting antipsychotics and only primary care physicians, not psychiatrists, appear to consider weight [138]. Only about a half or fewer of psychiatry residents report routinely screening for cardiometabolic risk factors and fewer still routinely treat these conditions [139]. A slight majority of psychiatry trainees view psychiatry as a primary care specialty and those that do are more likely to screen for diabetes and dyslipidemia [139]. While interest in primary care may vary, at least monitoring for the side effects of the very medications one is prescribing is expected [140], [141]. This has been attributed to a lack of knowledge among clinicians regarding the side effects of these medication, reported barriers to obtaining recommended measures (e.g., time or access to a scale or laboratory) and uncertainty about who is responsible for screening [140]. To resolve this, education about cardiometabolic effects of these medications and better integration of care are paramount. There is a growing movement to integrate other medical care into psychiatric teams, particularly those taking care of at-risk groups such as those with severe and persistent mental illness [142], [143].

The likelihood of early detection and institution of appropriate management for weight gain, dyslipidemia, insulin resistance and hypertension is increased if monitoring is incorporated into routine care. Those at higher risk for cardiometabolic syndrome will require closer monitoring. Side effects of psychotropic medications, especially weight gain, can lead to nonadherence. It is important, therefore, to monitor weight before and during treatment when any of the medications associated with weight gain are prescribed. If the patient is already overweight or obese, carefully consider all medication options. Early recognition is critical as weight gain within the first 4 weeks is a harbinger of continued weight gain. To manage treatment-emergent weight gain, clinicians must consider lowering doses, discontinuing medications or switching to alternative medications associated with fewer cardiometabolic side effects. Another option involves adding medications such as metformin and topiramate to either prevent or address weight gain [144]. Providers should also assess thyroid function and encourage lifestyle changes or dietary modification where applicable. Even prior to the onset of medication-induced cardiometabolic effects, primary preventive measures such as patient education, lifestyle modification and improved diet can also aid in averting their onset. This places the clinician in an active role in addressing excess cardiovascular morbidity and mortality in patients taking psychotropic medications.

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