

## Atypical antipsychotics: A review on the prevalence, monitoring, and management of their metabolic and cardiovascular side effects

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### Abstract

**Introduction:** Excessive weight gain, glucose intolerance, and dyslipidemia are well-known physical side effects of the metabolic syndrome commonly associated with atypical antipsychotic (AAP) treatment. We review these side effects of AAPs and their monitoring and management strategies.

**Methods:** A literature search was conducted to identify articles published on the prevalence, monitoring, and management of cardiometabolic side effects of AAPs.

**Results:** Comparative risk of AAPs on weight gain, hyperlipidemia, glucose intolerance, and QT interval corrected for heart rate prolongation varies across the AAPs currently available. Likewise, pharmacologic and nonpharmacologic options investigated for management of these side effects, and monitoring those at appropriate intervals, differ based on the clinical condition and risk factors identified.

**Discussion:** Atypical antipsychotics in general have little difference among them in short-term efficacy; however, the prevalence of their physical side effects substantially distinguishes them. It is of importance that clinicians carefully select AAPs bearing in mind the presence of risk factors, initiating patients directly on AAPs with a low risk of cardiometabolic side effects, and monitoring and managing those side effects at appropriate intervals.

**Keywords:** atypical antipsychotics, weight gain, hyperlipidemia, glucose intolerance, QTc prolongation

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### Introduction

During the last two decades, atypical antipsychotics (AAPs) have been increasingly popular among clinicians and patients because of the appealing decrease in extrapyramidal side effects in comparison with the first-generation antipsychotics.<sup>1</sup> These drugs, however, are associated with a significant side effect burden ranging

from metabolic disturbances, which include weight gain, type 2 diabetes, and dyslipidemia, to cardiovascular abnormalities, such as QT interval corrected for heart rate (QTc) prolongation.<sup>2</sup> Although the contribution of AAPs to an increase in mortality rates is controversial, data show that overall life expectancy is 11 to 20 years shorter among patients with bipolar disorder and schizophrenia.<sup>3</sup> In response to this growing issue, practice standards strongly encourage collaboration of medical disciplines to carefully monitor and manage these patients, so that they can receive the maximum benefit with minimal adverse effects.<sup>3,4</sup> Although studies have identified the correlation between AAPs and the elevation regarding cardiometabolic risks, there seems to be a lack of a comprehensive review of the prevalence of these risks and their management. Hence, this review is to identify

**TABLE 1: Comparative risk of atypical antipsychotics on weight gain<sup>7,8</sup>**

Risk Category	Antipsychotic Drug	Absolute Weight Gain, kg
High	Clozapine	5.3
	Olanzapine	1.03 to 4.3
Moderate	Amisulpride <sup>a</sup>	1.8
	Iloperidone	0.7 to 0.8
	Paliperidone	0.63 to 1.4
	Quetiapine	0.39 to 1.7
	Risperidone	2.5
	Sertindole <sup>a</sup>	3.1
Low	Aripiprazole	-3.6 to 0.13
	Asenapine	-1.4 to 1.2
	Lurasidone	-0.8 to 1.3
	Ziprasidone	-1.25 to -0.16

<sup>a</sup>Not available in the United States.

the prevalence of these physical side effects of AAPs, and to review the literature for monitoring and management strategies.

## Changes in Body Weight

The risk and magnitude of weight gain vary across the AAPs available, and they have been comparatively studied by several meta-analyses with consistency in results.<sup>5,6</sup> In the event a patient is experiencing unfavorable weight gain, a typical antipsychotic<sup>6,7</sup> or an alternative AAP should be considered (Table 1),<sup>7,8</sup> but clinicians should be

cognizant of higher discontinuation of treatment and unguaranteed loss of body weight.<sup>9,10</sup> Expert opinion indicates that the greatest amount of weight gain occurs within the first weeks of treatment and suggests that AAPs with a low risk of weight gain should be used at first initiation, whereas others should be reserved for situations of treatment resistance,<sup>8</sup> although weight gain is a possibility for those who are drug naive even on low-risk AAPs.<sup>8,10</sup> Genetics, lifestyle, and environmental factors, such as smoking, obesity, poor diet, and low levels of physical activity, may also play a prominent part despite the use of low-risk AAPs.<sup>11</sup> Apart from switching AAPs, other pharmacologic interventions have been investigated to reduce AAP-induced weight gain (Table 2).<sup>10,12-22</sup> For nonpharmacologic management of AAP-induced weight gain, both nutritional counseling and cognitive behavioral therapy are effective.<sup>23</sup> A review on cognitive behavioral therapy showed significant results in preventing and reversing AAP-induced weight gain, with a corresponding weight loss of 4.87 kg (95% confidence interval [CI], 2.6-7.1 kg) and 1.69 kg (95% CI, 0.6-2.8 kg), respectively.<sup>24</sup> A recent systematic review showed that exercise interventions, such as cycling, muscle strengthening, and walking programs, in adults with serious mental illness had no noticeable changes in body mass index and body weight.<sup>11</sup>

## Hyperlipidemia

Hyperlipidemia, characterized by elevated serum cholesterol or triglyceride concentrations, is found to have a direct association with AAP use,<sup>25</sup> although more recent work undertaken to better understand metabolic changes reveals fatty acid synthesis pathway deficits are present

**TABLE 2: Pharmacologic options investigated for management of antipsychotic-induced weight gain<sup>10,12-22</sup>**

Drug (Dosage)	Proposed Mechanism	Weight Change, kg (95% Confidence Interval) <sup>a</sup>
Amantadine (100-300 mg/d)	Decreases appetite; increase in dopamine release, inhibition of dopamine reuptake, and weak antagonism of <i>N</i> -methyl-D-aspartate-type glutamate receptors	-2.27 (-4.77 to 0.23)
Fluoxetine (60 mg/d)	Decreases appetite; selective inhibition of serotonin reuptake	0.99 (-0.90 to 2.88)
Metformin (750-2550 mg/d)	Weight regulation; increase in insulin sensitivity	-2.94 (-4.98 to -0.99) <sup>b</sup>
Nizatidine (150 mg bid)	Decreases appetite; inhibits histamine receptor-mediated gastric secretion and appetite stimulation	-2.07 (-4.58 to 0.45)
Orlistat (120 mg tid)	Weight regulation; decrease in intestinal fat absorption	-1.69 (-3.69 to 0.31)
Reboxetine (4 mg/d) <sup>c</sup>	Decreases appetite; selective inhibition of noradrenaline reuptake	-1.90 (-3.97 to -0.72) <sup>b</sup>
Sibutramine (up to 15 mg/d)	Appetite suppressant via inhibition of serotonin, noradrenaline and dopamine reuptake	-2.56 (-3.91 to -1.22) <sup>b</sup>
Topiramate (50 mg bid)	Decreases appetite; glutamatergic inhibition	-2.52 (-4.87 to -0.16) <sup>b</sup>

<sup>a</sup>Negative value favors intervention.

<sup>b</sup>Statistically significant.

<sup>c</sup>Not available in the United States.

**TABLE 3: Pharmacologic options investigated for management of antipsychotic-induced hyperlipidemia<sup>28-30</sup>**

Drug (Dose)	Proposed Mechanism	Remarks
Fibrates <sup>a</sup>	Activate PPAR- $\alpha$ —stimulating hepatic oxidation of free fatty acids and inducing expression of lipoprotein lipase, which hydrolyzes plasma lipids	Significant reduction in TG, TC, and LDL concentrations in patients treated with AAP Demonstrated a greater reduction in TG than statins
Metformin (1500 mg/d)	Activates AMP-activated protein kinase in hepatocytes, which in turn reduces acetyl-CoA carboxylase activity, induces fatty acid oxidation, and suppresses expression of lipogenic enzymes	Significant reduction in TG concentrations noted in olanzapine-treated patients
Omega-3 fatty acids (EPA 2-4 g/d)	Reduces concentration of Apo CIII, which increases activity of lipoprotein lipase, leading to increased clearance of plasma TG	Significant reduction in TG levels noted in clozapine-treated patients
Statins (mean atorvastatin equivalent of 18 $\pm$ 8.3 mg/d)	Inhibits HMG-CoA reductase, an enzyme that catalyzes the rate-limiting step in the biosynthesis of cholesterol	Reduction efficacy of 29% for TG, 36% for TC, and 49% for LDL in patients treated with AAP
Topiramate (100 mg/d)	Stimulates lipoprotein lipase in the adipose tissue and skeletal muscle, with a resultant increase in thermogenesis  Inhibits carbonic anhydrase enzymes involved in several steps of de novo lipogenesis	Prevention of olanzapine-associated increase in TG and other metabolic disturbances

AAP = atypical antipsychotic; AMP = adenosine monophosphate; EPA = eicosapentaenoic acid; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; LDL = low-density lipoprotein; PPAR- $\alpha$  = peroxisome proliferator-activated receptor  $\alpha$ ; TC = total cholesterol; TG = triglycerides.

<sup>a</sup>Dose not provided.

early in the course of schizophrenia and tend not to persist throughout its course.<sup>26</sup> Those AAPs that confer an increased risk of weight gain correlate with an increased risk of hyperlipidemia.<sup>25</sup> A comparative meta-analysis found olanzapine use was associated with greater increases in serum cholesterol more than aripiprazole, risperidone, and ziprasidone. Likewise,

quetiapine use was associated with greater increases in cholesterol than seen with risperidone and ziprasidone. There was no difference in producing an increase in cholesterol among patients prescribed clozapine, amisulpride, and quetiapine.<sup>27</sup> Those with raised cholesterol may benefit from dietary advice, lifestyle changes, and/or treatment with statins.<sup>7</sup> A variety of pharmacologic

**TABLE 4: Comparative risk of atypical antipsychotics on blood glucose<sup>7,36</sup>**

Risk Category	Drug	Change in Blood Glucose After 8 Weeks, mg/dL	Change in Blood Glucose After 14 Weeks, mg/dL
High	Clozapine	17.1	4.4 <sup>a</sup>
	Olanzapine	1.9 <sup>a</sup>	14.3
Moderate	Risperidone	-1.3 <sup>a</sup>	2.7 <sup>a</sup>
	Quetiapine		
Minimal	Aripiprazole		
	Amisulpride <sup>b</sup>		
	Asenapine		
	Lurasidone		
	Ziprasidone		

<sup>a</sup>Not statistically significant ( $P < .05$ ).

<sup>b</sup>Not available in the United States.

**TABLE 5: Risk factors for prolonged QT interval corrected for heart rate (QTc)<sup>42,43</sup>**

Older age (>70 y)
Female sex
Electrolyte disturbances (particularly hypokalemia and hypomagnesemia)
Congenital long QT syndrome/family history of sudden death
Personal history of heart murmur, shortness of breath with exertion, episodes of tachycardia at rest, irregular heartbeats, and especially syncope
Known cardiac disease: myocardial ischemia, congestive heart failure, cardiac arrhythmias
Bradycardia
Concomitant use of other medications known to prolong QTc interval
Concomitant medications known to inhibit metabolism of antipsychotics
Hepatic impairment
Endocrine and metabolic disorders
Central nervous system injury: stroke, infection, trauma

agents have been investigated for management of antipsychotic-induced hyperlipidemia (Table 3).<sup>28-30</sup>

## Glucose Intolerance

Individuals taking AAPs have a 2- to 3-fold increased prevalence in impaired glucose tolerance and diabetes compared with the general population.<sup>31</sup> Among the AAPs

in the market, there is an established link between diabetes and clozapine and olanzapine therapies, with fewer reports with quetiapine and risperidone.<sup>32</sup> A large study encompassing 2.5 million individuals showed a significantly greater risk of developing diabetes after 12 months in patients on clozapine (odds ratio [OR], 7.44; 95% CI, 0.60-34.75) or olanzapine (OR, 3.10; 95% CI, 1.62-5.93) treatment.<sup>33</sup> Patients taking risperidone had a nonsignificant increased risk of developing type 2 diabetes mellitus (T2DM) compared with nonantipsychotic users (OR, 2.2; 95% CI, 0.9-5.2) and those taking typical antipsychotics (OR, 1.6; 95% CI, 0.7-3.8).<sup>34</sup> A head-to-head meta-analysis found olanzapine produced a greater increase in blood glucose than amisulpride, aripiprazole, quetiapine, risperidone, and ziprasidone.<sup>27</sup> It is important to note that more recent work suggests direct effects of AAPs on insulin-sensitive tissues mediated by mechanisms independent of regulating eating behavior or appetite, and in the absence of psychiatric disease, weight gain, food intake, or hunger.<sup>35</sup>

If patients exhibit clinical signs and symptoms of hyperglycemia, clinicians should assess plasma glucose concentrations and consider medical or endocrine consultation, pharmacologic modification of the treatment regimen (eg, addition of hypoglycemic agents), active education of patients on lifestyle changes (eg, keeping active and having a low-carbohydrate, high-protein, and high-fiber diet), and the risks and benefits of switching the antipsychotic medication to one that carries less risk (Table 4)<sup>7,36</sup> of precipitating weight gain or T2DM.<sup>37</sup>

**TABLE 6: Comparative risk of QT interval corrected for heart rate (QTc) prolongation of atypical antipsychotics<sup>7,41</sup>**

Risk Category	Antipsychotic Drug	ECG Monitoring
High Established QTc prolongation of clinical concern, increased risk of TdP and sudden death <sup>c</sup>	Sertindole <sup>a,b</sup>	ECG monitoring recommended Avoid in patients with increased cardiac risk
Moderate Established QTc prolongation of clinical concern	Ziprasidone <sup>b</sup> Quetiapine <sup>b</sup>	ECG monitoring recommended in presence of risk factors
Low QTc prolongation of little or questionable clinical concern	Amisulpride <sup>a</sup> Aripiprazole <sup>b</sup> Asenapine <sup>b</sup> Clozapine <sup>b</sup> Iloperidone <sup>b</sup> Olanzapine <sup>b</sup> Paliperidone <sup>b</sup> Risperidone <sup>b</sup>	ECG monitoring recommended in presence of risk factors
Very low QTc prolongation not of clinical concern	Lurasidone	ECG monitoring recommended in drug overdose

ECG = electrocardiogram; TdP = torsades de pointes.

<sup>a</sup>Not available in the United States.

<sup>b</sup>Atypical antipsychotics with Food and Drug Administration warnings of QTc prolongation.

<sup>c</sup>QTc is a useful but imprecise indicator of risk of TdP and cardiac mortality.

**TABLE 7: Recommended monitoring guide for patients on atypical antipsychotics<sup>7,45,46</sup>**

Parameter	Baseline	First Month	Second Month	Third Month	Sixth Month	Annually	5 Years	Clinically Indicated
Medical history	✓					✓		✓
Waist circumference	✓			✓		✓		✓
Weight (body mass index)	✓	✓	✓	✓	✓	✓		✓
Blood pressure	✓			✓		✓		✓
Fasting lipids	✓			✓		✓	✓	✓
Fasting glucose or glycated hemoglobin	✓			✓		✓		✓
Electrocardiogram	✓							✓

## Cardiovascular Side Effects

The QTc interval in healthy adults ranges from 380 to 450 ms depending on age and gender, and a prolonged QTc interval (>450 ms in men and >460 ms in women) has been associated with increased cardiovascular risk.<sup>38</sup> QT prolongation is a known and established side effect of many medications, including certain AAPs, with the possibility of a QTc interval >500 ms increasing the risk of torsades de pointes (TdP), which can be potentially fatal.<sup>7,39</sup> However, TdP is known to occur at therapeutic doses of AAPs with a QTc interval <500 ms.<sup>40</sup> Thus, it can be challenging to determine the need to perform routine monitoring of QTc. This is due to the difficulty in establishing a threshold of clinical concern—when lower limits increase false positives and higher limits cause false negatives.<sup>41</sup>

Electrocardiogram (ECG) monitoring both prior to treatment and regularly thereafter is recommended for those with (1) an increased cardiac risk after medical evaluation, (2) an established increased risk of TdP and sudden death with the antipsychotic prescribed, and (3) an overdose of antipsychotic medication.<sup>41</sup> Patients at a higher risk (Table 5)<sup>42,43</sup> should be initiated with an antipsychotic with minimal QTc prolongation (Table 6).<sup>7,44</sup> If QTc prolongation is detected during treatment with AAPs, ECG should be repeated, and, if further prolonged, providers should continue to monitor ECG and serum electrolytes until stabilized. Discontinuation of the AAP and a referral to a cardiologist should be considered if there are persistent symptomatic complaints of syncope or palpitation.<sup>41</sup>

## Conclusion

Although the onset of weight gain, hyperlipidemia, and elevated glucose concentrations are known side effects of AAP-induced metabolic syndrome, patients with mental health disorders continue to receive these agents. Atypical antipsychotics in general have little difference among them in efficacy<sup>5</sup>; however, the prevalence of their physical side effects differentiates them substantially.

Therefore, the careful selection of an AAP is of essence, especially when a patient has a multitude of metabolic and cardiovascular risk factors. Antipsychotic polypharmacy is associated with an increased risk of these side effects and a longer duration of treatment with a greater severity (ie, higher body mass index).<sup>44</sup> It is of benefit to initiate patients directly on AAPs with a low risk of metabolic side effects or switch those who are already on a high-risk AAP to a low-risk AAP. Current literature demonstrates that several AAPs prolong QTc interval, possibly resulting in TdP and sudden cardiac death. Consideration of risk factors, suitable AAP drug choices, dietary modifications, initiating suitable pharmacologic interventions, and monitoring at appropriate intervals (Table 7)<sup>7,45,46</sup> with clinical end points are necessary to minimize the risk of metabolic and cardiovascular events of AAPs. In addition, metabolic and cardiovascular side effects outlined in this manuscript will likely apply to those newer AAPs; thus, it is of importance that clinicians coordinating care be vigilant of these cardiometabolic side effects and initiate standard management interventions promptly.

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