

# Clinical pearls for the monitoring and treatment of antipsychotic induced metabolic syndrome

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## Abstract

Antipsychotic medications increase the risk of metabolic syndrome, which then increases the risk of atherosclerotic cardiovascular disease and premature death. Routinely monitoring for signs of metabolic syndrome in patients taking antipsychotics allows for early detection and intervention. Psychiatric pharmacists can improve patient care through metabolic syndrome monitoring and recommendation of appropriate interventions. Monitoring for the metabolic adverse effects of antipsychotics, management of weight gain, and management of lipids and blood pressure are explored through 2 patient cases.

**Keywords:** antipsychotics, metabolic syndrome, weight, lipids, blood pressure, psychiatric pharmacist

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## Introduction

Patients with schizophrenia have significantly shorter life expectancies than the general population, largely due to cardiovascular mortality.<sup>1-3</sup> People with serious mental illness are more likely to smoke and eat unhealthy foods and less likely to exercise than the general population.<sup>4-7</sup> Lifestyle, genetic predisposition, and metabolic adverse effects (AEs) associated with antipsychotic medications also contribute to the development of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus.<sup>8</sup> Patients treated with antipsychotic medications

are 2 to 3 times more likely to meet criteria for metabolic syndrome, which is characterized by insulin resistance, obesity, dyslipidemia, and hypertension (Table 1).<sup>9,10</sup>

Antipsychotics are associated with different likelihoods of causing metabolic abnormalities. Clozapine and olanzapine are considered high risk, and chlorpromazine is considered medium-to-high risk. Quetiapine, risperidone, and paliperidone are considered medium risk, and asenapine, aripiprazole, lurasidone, ziprasidone, and haloperidol are considered low risk.<sup>11</sup> Newer antipsychotics, including cariprazine, brexpiprazole, and lumateperone appear to be low risk, and iloperidone appears to be medium risk.<sup>12,13</sup> Significant weight gain can occur within 6 to 8 weeks of starting any antipsychotic, and early weight gain may be a predictor of long-term weight gain.<sup>14,15</sup>

The mechanism responsible for metabolic abnormalities associated with antipsychotics is not fully understood and may be multifactorial. A few possible explanations include interference with hormonal control of food intake, antagonism or inverse agonism at serotonin 2C receptors (5-HT<sub>2c</sub>), antagonism at histamine receptors, polymorphisms in 5-HT<sub>2c</sub> receptors and leptin genes, antagonism at muscarinic M<sub>3</sub> receptors, and interference with

**TABLE 1: Criteria for diagnosis of metabolic syndrome<sup>10</sup>**

Risk Factor	Presence of 3 or More of the Following <sup>b</sup>
Waist circumference <sup>a</sup>	Men: 40 inches Women: ≥35 inches
Triglycerides	≥150 mg/dL OR Receiving treatment for elevated triglycerides
HDL	Men: <40 mg/dL Women: <50 mg/dL OR Receiving treatment for reduced HDL
Blood pressure	≥130 mm Hg systolic blood pressure OR ≥85 mm Hg diastolic blood pressure OR Receiving antihypertensive drug treatment
Fasting glucose	≥100 mg/dL OR Receiving treatment for elevated glucose

<sup>a</sup>Lower waist circumference cut-point in Asian American men (35 inches) and women (31 inches).

<sup>b</sup>Non-SI units maintained in certain aspects of this article for readability.

pancreatic  $\beta$ -cell receptors.<sup>16-19</sup> The metabolic disturbances are modifiable, so patients prescribed antipsychotics should receive baseline screening and ongoing monitoring to allow for early detection and intervention (Table 2).<sup>11</sup> The British Association for Psychopharmacology (BAP) *Guidelines on the Management of Weight Gain, Metabolic Disturbances, and Cardiovascular Risk Associated with Psychosis and Antipsychotic Drug Treatment* detail recommended approaches to monitoring for metabolic AEs during antipsychotic therapy and suggest possible intervention strategies when metabolic disturbances are detected.<sup>11</sup> Clinical application of potential treatment strategies for metabolic disturbances can be challenging. Selection of treatment requires taking into account multiple factors associated with the individual patient's psychiatric and physical status.

**TABLE 2: Recommended metabolic monitoring for antipsychotics<sup>a,11</sup>**

	Baseline	4 Weeks	8 Weeks	12 Weeks	6 Months	Annually
Weight/body mass index <sup>b</sup>	X	X	X	X	X	X
Fasting plasma glucose/hemoglobin A1c <sup>c</sup>	X			X	X	X
Lipids	X			X	X	X
Blood pressure	X			X	X	X

<sup>a</sup>Revisit all monitoring when clinically relevant if there is a change in antipsychotic medication.

<sup>b</sup>Ideally, monitor weekly for the first 4 to 6 weeks and then every 2 to 4 weeks up to 12 weeks.

<sup>c</sup>Hemoglobin A1c should be used to monitor blood glucose in the long term, but fasting plasma glucose may be a more appropriate measure in the early weeks of treatment.

### Take Home Points:

1. Lifestyle interventions are the first-line treatment approach for antipsychotic-induced weight gain and metabolic syndrome. Aripiprazole is studied as an intervention for weight gain with clozapine and olanzapine. Metformin is also studied as an adjunct to attenuate or reduce weight gain with antipsychotics. Weight reduction with aripiprazole and metformin is modest, so the potential risks and benefits should be considered prior to initiation.
2. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) are a first-line intervention for lipid lowering, especially for patients who fall into a statin benefit group. They are effective for increasing high-density lipoprotein and reducing total cholesterol, low-density lipoprotein, and triglycerides.
3. Thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) are first-line treatments for hypertension. In the context of metabolic syndrome, preference should be given to ACE inhibitors, ARBs, and CCBs because thiazide diuretics have the potential to increase blood glucose.

In this article, 2 cases explore the monitoring of metabolic AEs and the management of antipsychotic-associated elevations in weight, lipids, and blood pressure (BP). Management of elevated blood glucose (BG) is beyond the scope of this article; however, the American Diabetes Association guideline is an excellent resource for detection and management of elevated BG if further information is desired.<sup>20</sup>

### Case 1: Monitoring for Metabolic AEs

A 36-year-old patient presented for a 6-month follow-up to the pharmacist-led metabolic syndrome monitoring clinic, which was established to monitor for and treat metabolic AEs associated with antipsychotics. The patient was referred by the psychiatrist after being switched from

olanzapine to lurasidone 1 week prior due to weight gain. The past medical history was significant for bipolar I disorder, social anxiety disorder, tobacco use disorder, vitamin D deficiency, and obesity. Current medications included lurasidone 40 mg by mouth every evening, citalopram 40 mg by mouth daily, and cholecalciferol 2000 units by mouth daily. The patient was previously tried on divalproex sodium, which was switched to olanzapine 20 mg by mouth at bedtime due to lack of effectiveness. Even though mental health was stable on olanzapine, weight gain of approximately 14.5 kg in the first 6 months of treatment prompted the switch to lurasidone.

The patient smoked half a pack of cigarettes per day but denied alcohol or illicit drug use. There was no interest in smoking cessation services. The patient reported following a fairly healthy diet with consumption of lean meats, vegetables, fruits, water, and 1 (12-ounce) can of regular soda per day. Meals came from restaurants approximately once per month, but fast food was avoided. Exercise consisted of participation in water aerobics 3 times weekly (60 minutes per session).

Pertinent vital signs and fasting laboratory results from the appointment were as follows: height: 5 feet, 6 inches; weight: 100 kg; BMI: 35.8 kg/m<sup>2</sup>; BP: 111/77 mm Hg; pulse: 81 beats per minute (bpm); hemoglobin A<sub>1c</sub> = 5.4%; total cholesterol (TC) = 140 mg/dL; LDL = 71 mg/dL; triglycerides = 141 mg/dL; and HDL = 41 mg/dL.

Olanzapine is considered high risk for causing increases in weight, and lurasidone is considered low risk.<sup>11</sup> Lifestyle changes, such as smoking cessation, cessation of soda consumption, and increasing exercise to 5 days per week, were encouraged, but the patient was unable to successfully implement these changes. Lifestyle interventions are a first-line treatment approach for antipsychotic-induced weight gain<sup>11</sup> and metabolic syndrome.<sup>10</sup> Weight gain of  $\geq 7\%$  is considered clinically significant, and interventions for weight loss should be considered.<sup>11</sup> Weight loss of  $\geq 5\%$  of body weight decreases the risk for cardiovascular mortality.<sup>11</sup> The initial goal is to lose 5% to 10% of body weight within 6 months.<sup>21</sup> Patients should ideally exercise daily, but at least 30 minutes of moderate-intensity exercise 5 days per week should be encouraged.<sup>10</sup> Examples of moderate-intensity exercise include brisk walking (2.4 to 4 miles per hour), biking (5 to 9 miles per hour), ballroom dancing, active yoga, and recreational swimming.<sup>22</sup> Resistance training 2 days per week should also be encouraged. Caloric intake should be reduced, and the diet should be low in saturated fats, trans fats, cholesterol, sodium, and simple sugars.<sup>10</sup> An energy deficit of  $\geq 500$  kcal/d can typically be achieved with an intake of 1200 to 1500 kcal/d for women and 1500 to 1800 kcal/d for men.<sup>21</sup> The dietary approaches to stop

hypertension (DASH) diet is specifically recommended for weight loss in individuals with hypertension<sup>23</sup> and either the DASH or Mediterranean diet in patients with dyslipidemia.<sup>24</sup> Clinical experience indicates that it is often very challenging for this patient population to implement lifestyle changes due to poor insight, lack of finances, and living in group or nursing homes where meals are prepared for them.

There is no clear relationship between antipsychotic dose and weight gain, and clinical experience indicates that weight gain is possible even with low doses of antipsychotics.<sup>6,25</sup> Therefore, lowering the dose of olanzapine may not have been beneficial and could have led to mental health decompensation. The only antipsychotic tried for mood stabilization in this case was olanzapine. Switching to an antipsychotic with lower propensity for weight gain was a reasonable option, but risk of mental health destabilization was also a consideration.<sup>11</sup>

The BAP guidelines on management of weight gain and metabolic disturbances with antipsychotic drug treatment clearly outline the monitoring that should occur after an antipsychotic is initiated (Table 2).<sup>11</sup> Based on clinical experience, weight can change significantly between months 6 and 12 of antipsychotic treatment, so additional follow-up with the patient at month 9 to obtain weight/BMI and BP is helpful. The guidelines are less clear about how monitoring should be performed if there is a switch in antipsychotics and only state that “when clinically relevant, it is appropriate to revisit all of the monitoring steps.”<sup>11(p720)</sup> The term “clinically relevant” is not defined, but clinical experience indicates that restarting monitoring from the beginning is helpful when switching from a lower to a higher risk antipsychotic due to increased potential for weight gain. Continuing with the current monitoring plan may be appropriate when switching from a higher to a lower risk antipsychotic, especially if increasing the frequency of appointments is a burden to the patient.

This patient was switched from a high- to a low-risk antipsychotic, so a decision was made to continue with the current monitoring plan. Rather than restarting monitoring and checking weight in 4 weeks, weight and BP were rechecked in the metabolic clinic in 3 months. Weight loss of approximately 11.8 kg occurred during that time period and mental health remained stable.

## Case 1 Continued: Weight Management

The patient in case 1 returned to the metabolic clinic for the 12-month follow-up appointment. Approximately 25.9 kg were lost in the 6 months after transitioning from olanzapine to lurasidone (weight = 75 kg). However, mental health decompensated, and a manic episode

ultimately resulted in loss of custody of children and withdrawal from college education. The patient was admitted to the inpatient psychiatry unit 2 weeks prior and was switched from lurasidone back to olanzapine. Current medications included olanzapine 30 mg by mouth at bedtime and cholecalciferol 2000 units by mouth daily. The DASH diet<sup>26</sup> was followed prior to hospital admission, but exercise at the gym had stopped. Active substance use consisted of 3 cigarettes per day with a desire to quit. The patient was concerned about weight gain with olanzapine again and requested a weight loss medication.

Pertinent vital signs and fasting laboratory results from the appointment were as follows: height: 5 feet, 6 inches; weight: 77.7 kg; BMI: 26.6 kg/m<sup>2</sup>; BP: 113/79 mm Hg; pulse: 84 bpm; hemoglobin A1c = 5%; TC = 127 mg/dL; LDL = 45 mg/dL; triglycerides = 181 mg/dL; HDL = 46 mg/dL; alanine transaminase = 30 U/L; aspartate transaminase = 36 U/L; and creatinine clearance = 100 mL/min.

The BAP guidelines only support 2 medications as interventions for antipsychotic-induced weight gain: aripiprazole (for clozapine and olanzapine) and metformin.<sup>11</sup> Several other medications are studied but are not recommended by the guidelines for a variety of reasons: orlistat is associated with high rates of discontinuation; topiramate use is limited by its AEs; glucagon-like peptide-1 receptor agonists (eg, liraglutide) do not have enough data for use in people taking antipsychotics; amantadine, melatonin, and zonisamide data are too limited; and atomoxetine, dextroamphetamine, famotidine, fluoxetine, fluvoxamine, and nizatidine failed to show benefit.<sup>11</sup>

Aripiprazole is studied as an adjunct to clozapine and olanzapine for weight management and clinical efficacy.<sup>27-29</sup> Aripiprazole doses in the studies range from 5 to 30 mg daily, and there are statistically significant differences in weight loss over placebo of around 2 kg. The most common AEs reported were nausea, headache, insomnia, anxiety, and restlessness. Schizophrenia symptom scores did not change significantly with combination treatment.<sup>27-29</sup> There is insufficient evidence to support aripiprazole augmentation of other antipsychotics.<sup>11</sup> A challenging aspect about using aripiprazole for this purpose is that it can also cause weight gain for some patients. Data from the aripiprazole prescribing information indicates 8.1% of patients with schizophrenia, 2.2% of patients with bipolar disorder, and 5.2% of patients with MDD gained  $\geq 7\%$  of their body weight in placebo-controlled trials.<sup>30</sup> Based on clinical experience, aripiprazole can cause weight gain in some patients, and the risks associated with antipsychotic polypharmacy may outweigh the potential benefit of modest weight loss.

Metformin can be used to attenuate or reduce weight gain with antipsychotics, and its use is recommended after lifestyle interventions have been fully explored.<sup>11</sup> The reduction in weight is modest in studies (approximately 2 to 3 kg).<sup>31-33</sup> Clinical experience indicates that patients are unlikely to lose more than 5 kg after metformin initiation, especially if lifestyle changes are not implemented. Metformin is also shown to attenuate weight gain by up to 5 kg in individuals who are initiating an antipsychotic for a first episode.<sup>34</sup> Study data can be difficult to interpret and apply because many were conducted outside of the United States, different methodologies were used, small numbers of participants were included, and trials were of short duration. Common AEs reported in studies<sup>31-34</sup> mirror what is seen in practice: nausea, bloating, abdominal pain, and diarrhea. Metformin is contraindicated in patients with an estimated glomerular filtration rate less than 30 mL/min, and initiation is not recommended when estimated glomerular filtration rate is between 30 and 45 mL/min. Excessive alcohol intake and hepatic impairment can also increase the risk for metformin-induced lactic acidosis.<sup>35</sup>

Despite some of its limitations, metformin can be particularly useful in patients who require treatment with an antipsychotic and also have prediabetes or diabetes.<sup>20</sup> Metformin can also be safely used for weight management in patients with normal BG levels.<sup>32</sup> A range of metformin doses (500 to 2550 mg/d) are used in studies, but clinical experience indicates that titrating the dose up to 2000 mg/d is beneficial. The optimal duration of metformin use is not clear. The American College of Cardiology and American Heart Association (ACC/AHA) obesity guidelines indicate that discontinuation of a weight loss medication should be considered after 12 weeks on a maximal dose if the patient loses less than 5% initial body weight.<sup>21</sup> Due to 1 study showing weight loss benefit in the metformin group for up to 5 months, the BAP guidelines state that there should be a reasonable trial of metformin to demonstrate maximum effect.<sup>11,33</sup> Based on clinical experience and the amount of time it takes to titrate metformin, consider discontinuing the medication after 6 months of treatment if solely being used for weight loss and no benefit is observed. Continuing metformin for the duration of antipsychotic treatment may be helpful if metformin is effective for attenuation of weight gain and it is well tolerated.

Although use of topiramate for antipsychotic-induced weight gain is not recommended by the BAP guidelines, it has some evidence to support its use. There are 4 double-blind, placebo-controlled randomized trials<sup>36-39</sup> ranging from 8 to 12 weeks in length. Weight loss or attenuation was modest and ranged from 1.27 to 5.6 kg. However, topiramate was associated with significant AEs including psychomotor slowing, paresthesia, dizziness, and head-

ache.<sup>36-39</sup> Bupropion/naltrexone and phentermine/topiramate are approved by the FDA for weight loss but have not been studied for antipsychotic-induced weight gain. In addition, there are warnings/precautions for suicidal behavior and ideation with these medications.<sup>40,41</sup> Single-ingredient bupropion has very limited evidence to support its use in this patient population. One small study<sup>42</sup> including 8 subjects demonstrated bupropion could reduce olanzapine-associated weight gain by 3.4 kg.

In addition to recommended lifestyle changes, the patient in this case was initiated on metformin to help prevent antipsychotic-induced weight gain. Renal and hepatic function were within normal limits, and there was no alcohol consumption. The hemoglobin A<sub>1c</sub> was normal, but metformin could still be safely used. Sustained-action metformin 500 mg daily was started and education to take it with food was provided. The dose was slowly titrated, but the patient was unable to tolerate it due to gastrointestinal AEs and ultimately decided to discontinue it. Aripiprazole could have been considered as an adjunct to olanzapine, but the patient and providers preferred to avoid polypharmacy with multiple antipsychotics. The providers preferred not to use topiramate due to concern that risk for cognitive AEs may outweigh the potential benefits in this patient who hoped to return to college and regain custody of the children. Bupropion may have been an interesting option to help with weight and smoking cessation, but the providers were concerned about the potential for inducing mania. In addition, bupropion has not been well studied for antipsychotic-induced weight gain. The patient preferred to continue olanzapine monotherapy despite gaining approximately 27 kg within 6 months of initiation because of the mental health benefits. The pharmacist in the metabolic clinic continued to work with the patient on diet and exercise.

## Case 2: Lipid and BP Management

A 48-year-old white male presented to the clozapine clinic for routine follow-up and monitoring. The past medical history was significant for schizoaffective disorder; tobacco use disorder; constipation; vitamin D deficiency; and metabolic syndrome characterized by obesity, dyslipidemia, and prediabetes. Current medications included clozapine 150 mg by mouth at bedtime, aspirin 81 mg by mouth daily, docusate 100 mg by mouth twice daily, and cholecalciferol 2000 units by mouth daily. He tried and failed multiple antipsychotics prior to initiation of clozapine 4 years ago. His mental health had been stable since initiating clozapine, and he resides in a group home. He gained 9.5 kg the year after clozapine was initiated, and then weight stabilized. He had difficulty controlling his diet at the group home and ate what was prepared for him. Despite lifestyle education, he continued to visit the

vending machine frequently for soda (2 cans per day), candy bars (1 per day), and chips (1 bag per day). He was referred to a dietitian but was unable to successfully implement dietary changes. He did not have access to exercise equipment at his group home and did not walk outside due to inclement weather. He was referred to an exercise program located in the same facility as the clozapine clinic but did not attend the appointments. Metformin initiation for weight management and prediabetes was recommended at several appointments, but he declined because he preferred not to take more medications. He smoked half a pack of cigarettes per day and was not interested in smoking cessation services.

His resting BP was elevated at his past 2 appointments (136/84 and 136/86 mm Hg), so the nurse at his group home had been recording daily BP readings in a log. His BP log revealed an average BP of 138/86 mm Hg. Pertinent vital signs and fasting laboratory results from the appointment were as follows: height: 5 feet, 10 inches; weight: 104.5 kg; BMI: 33 kg/m<sup>2</sup>; BP: 138/88 mm Hg; pulse: 79 bpm; hemoglobin A<sub>1c</sub> = 6%; TC = 225 mg/dL; LDL = 136 mg/dL; triglycerides = 395 mg/dL; HDL = 27 mg/dL; clozapine level = 132 mcg/L; norclozapine level = 135 mcg/L; white blood cell count = 8.4 thousand cells/mcl; and absolute neutrophil count = 5.1 thousand cells/mcl.

Clozapine is considered high risk for causing increases in weight, lipids, BG, and BP.<sup>11</sup> This patient had already tried and failed multiple antipsychotics, and his mental health had been stable for 4 years on clozapine. Switching to an antipsychotic with lower liability for metabolic AEs is likely not a feasible option for this patient. Lifestyle interventions are a first-line treatment approach, but the patient had been unsuccessful with altering his diet, exercising, or attempting smoking cessation. Therefore, medically treating the metabolic AEs was necessary.<sup>11</sup>

## Lipids

Hydroxymethylglutaryl-CoA reductase inhibitors (statins) are considered the cornerstone of treatment for lipid lowering due to evidence demonstrating they can prevent ASCVD. There are 4 categories of patients that may benefit from statin therapy, including those with clinical ASCVD, LDL  $\geq$ 190 mg/dL, diabetes aged 40 to 75 years, and estimated 10-year ASCVD risk score  $\geq$ 7.5%.<sup>24</sup> An online ASCVD risk estimator can be located at <http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#/calculate/estimate/>.<sup>43</sup> Individuals with an ASCVD risk score of 7.5% to <20% are considered intermediate risk for a cardiovascular event, and a moderate-intensity statin can be initiated if risk enhancers favor it. Examples of risk-enhancing factors include but are not limited to metabolic syndrome, chronic kidney disease, inflamma-

**TABLE 3: Statin intensity based on daily dosing<sup>24</sup>**

High Intensity	Moderate Intensity	Low Intensity
<ul style="list-style-type: none"> <li>• Atorvastatin 40 mg, 80 mg</li> <li>• Rosuvastatin 20 mg, 40 mg</li> </ul>	<ul style="list-style-type: none"> <li>• Atorvastatin 10 mg, 20 mg</li> <li>• Fluvastatin 40 mg twice daily</li> <li>• Fluvastatin XL 80 mg</li> <li>• Lovastatin 40 mg, 80 mg</li> <li>• Pitavastatin 1 mg, 2 mg, 4 mg</li> <li>• Pravastatin 40 mg, 80 mg</li> <li>• Rosuvastatin 5 mg, 10 mg</li> <li>• Simvastatin 20 mg, 40 mg</li> </ul>	<ul style="list-style-type: none"> <li>• Fluvastatin 20 mg, 40 mg</li> <li>• Lovastatin 20 mg</li> <li>• Pravastatin 10 mg, 20 mg</li> <li>• Simvastatin 10 mg</li> </ul>

tory disease (rheumatoid arthritis, psoriasis, HIV), ethnicity (eg, South Asian ancestry), and persistently elevated triglycerides ( $\geq 175$  mg/dL). Individuals with an ASCVD risk score  $\geq 20\%$  are considered high risk, and statin initiation should be considered with a goal to reduce LDL by at least 50%. Moderate-intensity statins are expected to lower the LDL by 30% to 49% and high-intensity statins by  $\geq 50\%$  (Table 3).<sup>24</sup>

Statin are most effective for lowering LDL, but they can also lower triglycerides (22% to 45%) and increase HDL (5% to 10%).<sup>44</sup> Fibrates and niacin are effective for reducing triglycerides but have a mild LDL-lowering effect, and there is not enough evidence to routinely support their use as add-on medications to a statin.<sup>24</sup> Adding a fibrate or omega-3 fatty acids to a statin is recommended for patients with persistently elevated severe hypertriglyceridemia ( $\geq 500$  mg/dL) to prevent pancreatitis. Fenofibrate is preferred over gemfibrozil in patients being treated with a statin due to lower risk of myopathy.<sup>24</sup> The dose of the statin is another important consideration. The largest percentage of LDL lowering is achieved with the initial dose.<sup>45,46</sup> Each doubling of the statin dose should then lead to an additional 4% to 7% reduction in LDL.<sup>45,46</sup> Clinical experience indicates that starting statins at a low dose and titrating up does not lead to the same level of LDL lowering as starting at a moderate- to high-intensity dose. Initiation of a lower intensity statin may be considered if there is a history of statin intolerance.

## Blood Pressure

Stage 1 hypertension is defined as systolic BP 130 to 139 or diastolic BP 80 to 89 mm Hg. Stage 2 hypertension is defined as BP  $\geq 140/90$  mm Hg.<sup>23</sup> At least 2 resting BP readings obtained on 2 separate occasions should be used to estimate the BP. A log of home BP readings can provide a more accurate estimation of BP if proper techniques are used.<sup>23</sup> For primary prevention of cardiovascular disease in adults, nonpharmacologic therapy and treatment with an antihypertensive is recommended for individuals with stage 2 hypertension or stage 1 hypertension and a 10-year ASCVD risk of 10% or higher. Initiation of 2

antihypertensive agents from different classes is recommended for individuals with stage 2 hypertension. A BP target of  $<130/80$  mm Hg is recommended.<sup>23</sup> Thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) are first-line treatments for hypertension due to evidence demonstrating that they reduce clinical events. There is inadequate evidence to support beta blockers as a first-line treatment for hypertension in the absence of certain cardiovascular comorbidities, such as heart failure or ischemic heart disease. Patient-specific factors, such as comorbidities, concurrent medications, age, race, and medication adherence, should be taken into consideration when selecting an initial antihypertensive.<sup>23</sup>

The optimal treatment for hypertension in individuals with metabolic syndrome has not been clearly defined. Thiazide diuretics can increase insulin resistance and accelerate conversion to diabetes mellitus.<sup>23,47,48</sup> They can also worsen dyslipidemia.<sup>23,49</sup> The European Society of Cardiology and the European Society of Hypertension guidelines list metabolic syndrome as a possible contraindication for use of thiazide diuretics.<sup>48</sup> The ACC/AHA guidelines note that small increases in BG levels are possible but also state there are no data available demonstrating deterioration in cardiovascular outcomes in patients with metabolic syndrome who are treated with thiazide diuretics.<sup>23</sup> When no compelling indications or contraindications are present to help guide treatment selection, preference may be given to an ACE inhibitor, ARB, or CCB in patients with metabolic syndrome to help avoid increases in BG. Age and race can also help with treatment selection. Thiazide diuretics and CCBs are preferred in Black adults without heart failure or chronic kidney disease because they are more effective than ACE inhibitors or ARBs.<sup>23</sup> Older adults may also respond better to thiazide diuretics and CCBs due to a declining number of nephrons and lower plasma renin levels.<sup>50</sup>

Using an average BP of 138/86 mm Hg, the patient in this case had a 10-year ASCVD risk score of approximately 17.5%, placing him into a statin benefit group. His known risk-enhancing factors included metabolic syndrome,

characterized by persistently elevated triglycerides, obesity, and elevated BP. He also smoked cigarettes. Lifestyle modifications continued to be encouraged, and a risk-benefit discussion about statin therapy was conducted. He was willing to initiate a statin and was started on atorvastatin 20 mg by mouth daily. A moderate-intensity statin was appropriate based on his 10-year ASCVD risk score. His triglycerides were elevated but not enough to warrant addition of a nonstatin therapy. His BP readings in the clinic and at home indicated he had stage 1 hypertension, and his 10-year ASCVD risk score was greater than 10%. The patient did not have any compelling indications or contraindications to help guide selection of an antihypertensive. Given his age, race, and history of metabolic syndrome, initiation of an ACE inhibitor, ARB, or CCB may be most appropriate. After review of the potential AEs associated with each medication class, the patient elected to start amlodipine 5 mg by mouth daily.

## Conclusion

Patients taking antipsychotics are at increased risk for developing metabolic syndrome, which subsequently increases their risk for ASCVD. Weight, fasting plasma glucose/A1c, lipids, and BP should be routinely monitored in patients taking antipsychotics. Psychiatric pharmacists can improve patient care by conducting or assisting with this monitoring and recommending interventions when necessary. Lifestyle changes with diet and exercise are a first-line treatment approach but are often difficult for patients to implement. Switching to an antipsychotic with lower propensity for metabolic AEs is not always an option due to risk for mental health decompensation. In addition, there remains some risk for metabolic AEs with the low-risk antipsychotics. Medically treating the metabolic AEs may be necessary. Aripiprazole (for olanzapine and clozapine) and metformin have the most evidence to support their use for antipsychotic-induced weight gain, but weight loss in studies is modest. The potential risks and benefits should be evaluated and patient preference taken into consideration before initiating a medication for weight loss. Statins are considered the cornerstone of treatment for lipid lowering, especially for patients who fall into a statin-benefit group. First-line antihypertensive medications are thiazide diuretics, ACE inhibitors, ARBs, and CCBs. For patients with metabolic syndrome, preference may be given to an ACE inhibitor, ARB, or CCB to help avoid increases in BG that can occur with thiazide diuretics.

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