Metabolic Health as an Essential Consideration When Using Antipsychotic Medications

Key Messages

- **Avoid unnecessary risk: Antipsychotic medications should only be used when clinically indicated.**
- **Know your patient: Determine the metabolic baseline of every patient when initiating or changing an antipsychotic medication. Routinely monitor all patients prescribed antipsychotic medications.**
- **Minimize avoidable risks whenever possible: Select antipsychotic medications with more favorable metabolic profiles, especially in patients who are at risk for metabolic syndrome.**
- **Manage antipsychotic-induced metabolic changes as clinically indicated: Collaboration and effective communication among patients, their support networks, and all treating providers should occur to optimize patient care.**

At the conclusion of this activity, participants will be able to:

- Discuss the metabolic side effects associated with use of antipsychotic medications;
- Identify appropriate monitoring parameters and schedules for metabolic side effects in patients treated with antipsychotic medications; and
- Describe strategies for the management of metabolic side effects of antipsychotic medications.

Introduction

Antipsychotic medications have a role in the medical management of psychiatric symptoms in a wide variety of conditions.[1] They comprise several agents, which may be grouped into the following categories: typical or first-generation antipsychotics (FGAs); or atypical or second-generation antipsychotics (SGAs). While exact mechanisms are still unknown, antipsychotic medications have varying effects on neurotransmitter systems.[2] Generally, FGAs have high dopamine receptor D2 antagonism and low serotonin-2A receptor antagonism (5-HT_{2A}).[2,3] SGAs have moderate-to-high D2 antagonism and high 5-HT_{2A} antagonism. Antipsychotic medications also vary in their effects on alpha-adrenergic, histaminic, and muscarinic receptors. These differences in receptor interactions and patient response result in a range of therapeutic effects and side effect profiles.

Antipsychotic medications should only be used when clinically indicated. Table 1 summarizes selected indications for oral formulations of antipsychotic medications approved by the Food and Drug Administration (FDA) for use in adults. When an antipsychotic medication is identified as a necessary component of a person-centered treatment plan, monitoring for medication adherence, effectiveness, and side effects should occur.[4] When selecting a specific antipsychotic regimen, especially when choosing between the first- and second-generation agents, relative risks of side effects are important considerations.[5] The 4 major side effects of these drug classes are: extrapyramidal symptoms, weight gain/metabolic effects, prolactin elevation/sexual side effects, and QTc prolongation. This continuing education activity will focus on antipsychotic-induced weight gain and associated cardiometabolic side effects.

Table 1. FDA-approved indications for oral formulations of antipsychotic medications in adults[6,7]

Indications	Antipsychotic Medications	
Agitation associated with Alzheimer's disease	SGA	brexpiprazole
Bipolar I disorder	SGA	aripiprazole, asenapine, cariprazine, iloperidone, olanzapine, olanzapine/samidorphan, quetiapine, quetiapine XR, risperidone, ziprasidone
Bipolar depression	SGA	cariprazine, lumateperone, lurasidone, olanzapine in combination with fluoxetine, quetiapine, quetiapine XR
Major depressive disorder (adjunctive treatment)	SGA	aripiprazole, brexpiprazole, cariprazine, olanzapine in combination with fluoxetine, quetiapine XR
Parkinson's disease psychosis	SGA	pimavanserin
Schizophrenia	FGA	chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, prochlorperazine, thioridazine[a], thiothixene, trifluoperazine
	SGA	aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine[a], iloperidone, lumateperone, lurasidone, olanzapine, olanzapine/samidorphan, paliperidone, quetiapine, quetiapine XR, risperidone, ziprasidone
Tourette's syndrome	FGA	haloperidol, pimozide

FDA=Food and Drug Administration; FGA=first-generation antipsychotic; SGA=second-generation antipsychotic; XR=extended-release
[a] Treatment resistant schizophrenia

Antipsychotic Medications and Cardiometabolic Risk

Antipsychotic medications may induce or worsen metabolic abnormalities such as weight gain, glucose dysregulation, and hyperlipidemia.[1] Additionally, populations in which antipsychotic medications are used experience conditions such as obesity, diabetes mellitus, and cardiovascular disease with greater frequency than the general population.[8-10] Whether the metabolic disturbances are a function of the treatment or the disease itself, the likelihood of an antipsychotic medication exacerbating an existing health condition should be considered at the time of treatment selection, as some antipsychotics carry greater risks of inducing certain side effects compared to others.[1,4,5] While FGAs may have lesser impact on metabolic changes

compared to SGAs, they are associated with other side effects, such as extrapyramidal symptoms, that may be disabling. A summary of the relative metabolic side effect profiles of antipsychotic medications can be found in Table 2.

Table 2. Metabolic side effect profiles of antipsychotics (from 2023 Department of Veterans Affairs/Department of Defense Summary Clinical Practice Guidelines for Management of First-Episode Psychosis and Schizophrenia)[11]

Antipsychotic	Weight gain	Metabolic effects*
First generation		
Chlorpromazine	+++	++
Fluphenazine	+	+
Haloperidol	+	+
Loxapine	+	+
Molindone	+	+
Perphenazine	++	+
Pimozide	+	+
Thioridazine	++	+
Thiothixene	+	+
Trifluoperazine	+	+
Second generation		
Aripiprazole	0/+	0/+
Asenapine	+	+
Brexpiprazole	0	+
Cariprazine	+	+
Clozapine	+++	+++
Iloperidone	++	+
Lumateperone	0	+
Lurasidone	+	+
Olanzapine	+++	+++
Olanzapine/samidorphan	++	+++
Paliperidone	++	+
Pimavanserin	0	0
Quetiapine	++	++
Risperidone	++	++
Ziprasidone	+	+

Key: +++ = strong effect; ++ = moderate effect; + = minimal effect; 0 = no effect
* Metabolic effects = Glucose dysregulation, dyslipidemia, increased waist circumference

Metabolic Monitoring for Patients Treated with Antipsychotic Medications

In 2004, the American Diabetes Association (ADA), American Psychiatric Association (APA), American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity published a consensus statement that has served as the foundational reference for early and regular metabolic monitoring of patients treated with antipsychotic medications.[1] Since then, laboratory monitoring practices have expanded to include more non-

fasting testing options. For example, in 2010 the ADA added glycosylated hemoglobin (A1c) as an acceptable diagnostic test for diabetes mellitus.[12] Table 3 summarizes an evidence-based schedule for metabolic monitoring.

Table 3. Metabolic monitoring recommendations (adapted from ADA/APA consensus statement*)[1]

Parameters	Frequency					
	Baseline	Week 4	Week 8	Week 12	Every 3 months	Yearly
	After initiating or changing antipsychotic medication				*Ongoing monitoring*	
Personal/family history	X					X
Weight, BMI	X	X	X	X	X	
Waist circumference	X					X
Fasting plasma glucose or A1c	X			X		X
Lipid panel	X			X		X[a]
Blood pressure, heart rate	X			X		X

A1c=glycosylated hemoglobin; BMI=body mass index
* More frequent monitoring may be necessary based on individual clinical circumstances
[a] Annually in patients at higher cardiovascular risk; every 5 years for patients at lower cardiovascular risk

In 2020, the APA published an updated practice guideline for the treatment of patients with schizophrenia which further discusses the evidence for baseline and regular monitoring of concomitant physical conditions and medication side effects in patients with severe mental illness.[4] The APA recommends monitoring based on the individual clinical circumstances such as the side effect profile of the medication(s) being used, the addition or modification of other medications with metabolic effects, and the patient's history.

Personal/family history

Baseline screening for metabolic risk is recommended when initiating or changing an antipsychotic medication.[1,4] Baseline assessment includes screening for a personal and family history of obesity, diabetes (and diabetes risk factors), dyslipidemia, hypertension, and cardiovascular disease. Examples of other information to collect include current medications (and side effects of these medications) and a list of the other healthcare professionals with whom the patient has established care. This is also an opportunity to address modifiable risk factors which impact cardiovascular health, such as tobacco use, diet, and physical activity levels.

Weight gain

Obesity increases the risk of cardiovascular adverse events.[13] Compared to the general population, persons with severe mental illness are 2 to 3 times more likely to have overweight or obesity.[14] Symptoms of mental illness can contribute to physical inactivity, excessive caloric

intake, and the consumption of diets high in saturated fat and sugar.[15,16] Some antipsychotic medications are also associated with risk of clinically significant weight gain (defined as ≥7% of baseline weight), with a few agents carrying especially elevated risks.[11,17-20] While there is variability in the amount of weight an individual patient may gain on a specific antipsychotic medication, clozapine and olanzapine are associated with the highest weight gain.[4] Weight gain can also be greater when initiating antipsychotic medications in antipsychotic-naïve patients than when changing antipsychotic medications.[21] Children and adolescents are especially at risk of greater weight gain and long-term health effects.[22] The mechanism of weight gain appears related to histamine H1 receptor antagonism, with serotonin and muscarinic receptors also thought to play a role.[4] Weight gain is often observed within the first 6 months after initiation of an antipsychotic medication but can also occur later in treatment, with some patients continuing to gain weight indefinitely.[4,23]

Body mass index (BMI) can be calculated using a patient's height and weight and is a convenient tool to screen for overweight and obesity. Body weight, height, and BMI should be determined at baseline.[1,4] After an antipsychotic medication is initiated or changed, weight and BMI should be monitored at every visit for the first 6 months and at least quarterly thereafter.[4]

Due to the limitations of BMI in measuring excess body fat, use of additional measures is recommended to appropriately assess weight and distribution of adiposity. In adults, a combination of BMI and waist circumference may be more useful to assess weight-related health risks.[24] The 2004 ADA/APA consensus statement recommends measuring waist circumference (at the level of the umbilicus) at baseline and at least annually.[1] More recent guidance recommends assessing for metabolic syndrome at baseline, 4 months after starting or changing an antipsychotic medication, and annually thereafter.[4] American Heart Association (AHA) criteria for metabolic syndrome are summarized in Figure 1.

Figure 1. Metabolic syndrome defined by ≥3 of the following:[13]

1. Waist circumference ≥88 centimeters (cm) for women and ≥102 cm for men (if Asian ancestry, ≥80 cm for women and ≥90 cm for men);
2. High-density cholesterol <40 mg/dL for men and <50 mg/dL for women;
3. Triglycerides ≥150 mg/dL;
4. Elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg and/or use of antihypertensive medications); and
5. Fasting blood glucose ≥100 mg/dL.

Glucose and type 2 diabetes mellitus

Glucose abnormalities may be induced or exacerbated by antipsychotic medications.[1] For example, clozapine and olanzapine are associated with an increased risk of diabetes.[25,26] Additionally, all SGA product labels include warnings about the risk of hyperglycemia and diabetes mellitus.[6,7] While the mechanism of antipsychotic-associated hyperglycemia is uncertain, there is evidence of disturbances in fasting plasma glucose (FPG) and/or glucose tolerance.[27] These effects can occur within a few weeks of initiating an antipsychotic medication, even in the absence of weight gain; however, antipsychotic-associated weight gain is well-documented and can further contribute to the risk of type 2 diabetes. Additionally, in patients with schizophrenia, genetic predisposition may influence diabetes risk,[28] as well as other known diabetogenic factors such as a sedentary lifestyle, poor diet, or tobacco use.[29]

Since glucose abnormalities may be present prior to treatment with an antipsychotic medication,[30-32] initial or baseline assessments for these abnormalities should be conducted.[1,4]

An initial assessment includes reviewing diabetes risk factors (Figure 2) and screening using FPG, A1c, or oral glucose tolerance test (OGTT). Continued monitoring for prediabetes or diabetes using FPG, A1c, or OGTT is recommended 12 to 16 weeks after initiating a new antipsychotic medication and at least annually thereafter.[1,4] More frequent monitoring may be needed if weight changes occur, symptoms of diabetes are present, or a random plasma glucose exceeds 200 mg/dL. More information about improving health outcomes for patients at risk of developing diabetes can be found in the MPEP activity "Prediabetes Screening and Management".

Figure 2. Risk factors for prediabetes or diabetes in asymptomatic adults[33]
• Increasing age (screening for prediabetes should begin in all adults at age 35) • Overweight or obese (BMI ≥25 kg/m^2) • First-degree relative with diabetes (e.g., parent, sibling) • African American, Asian American, Latino, Native American, or Pacific Islander ethnicity • History of cardiovascular disease • BP ≥130/80 mmHg, or use of an antihypertensive agent • HDL-C <35 mg/dL and/or triglyceride level >250 mg/dL • Physical inactivity (adults who are physically active less than 3 times per week) • History of gestational diabetes or has given birth to a child who weighed over 9 pounds • History of PCOS • People with HIV • Taking a medication known to increase the risk of prediabetes or diabetes • History of pancreatitis

BMI=body mass index; BP=blood pressure; HDL-C=high-density lipoprotein cholesterol; HIV=human immunodeficiency virus; PCOS=polycystic ovary syndrome

Early detection and appropriate treatment should be implemented in accordance with the most recent guidance documents such as those published by the American Diabetes Association or the American Association of Clinical Endocrinology.

Lipids

Antipsychotic medications have varying effects on total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and plasma triglycerides (TG).[34] Some antipsychotic medications have demonstrated no effects on lipids, while others such as quetiapine and olanzapine have shown increases in TC, LDL-C, and TG.[4] The exact mechanism of antipsychotic-associated lipid abnormalities is unknown. However, lipid disturbances can occur soon after the initiation of an antipsychotic medication (within 4 weeks), even before the presence of clinically significant weight gain, warranting timely monitoring and intervention.[35] Antipsychotic-naïve patients may already have lipid abnormalities at baseline.[36] If a fasting lipid panel cannot be obtained, a non-fasting lipid panel is reasonable for screening.[37] A lipid panel should be performed at baseline and repeated at 12 to 16 weeks after initiation of the antipsychotic medication.[1,4] Additional information on screening and management of individuals with lipid abnormalities can be found in national guidelines.

Blood pressure and heart rate

Metabolic disturbances related to antipsychotic medication use can also include blood pressure changes. Antipsychotic medications have been associated with orthostatic changes in blood pressure. Orthostatic hypotension is dose-related and results from alpha-receptor blocking effects, with clozapine and iloperidone noted as having high risks of orthostasis.[4,38,39] It should also be considered that excessive weight gain and obesity can contribute to increased rates of

hypertension.[4] Blood pressure and heart rate should be measured at baseline with regular follow-up assessments as clinically indicated.

Minimizing Avoidable Risks

Action should be taken to minimize metabolic-related risks of antipsychotic medications whenever possible. One opportunity for intervention is at the time of drug selection. As discussed earlier and summarized in Table 2, antipsychotic medications with more favorable metabolic profiles are available for use in patients at high risk of metabolic complications. Using the lowest effective dose of an antipsychotic medication can also lessen the harm from treatment.[4]

Some antipsychotic medications are available in long-acting injectable (LAI) dosage forms. While LAI antipsychotics have not been shown to reduce metabolic risks,[40] they can help improve medication adherence and may be preferred by some patients.[4] When initiating an LAI antipsychotic, it is important to limit drug exposure to clinically necessary usage. For example, the duration of overlap between oral and LAI medications should not exceed manufacturer and evidence-based recommendations.

Although the rationale for metabolic monitoring remains clear and consistent, monitoring rates have been shown to be less than optimal, regardless of antipsychotic formulation.[41-44] Barriers to routine monitoring have been identified at the system, provider, and patient levels.[45] Examples of barriers include: fragmented communication between providers, time constraints, transportation problems, or patient views and behaviors. Just as effective communication among mental health, primary care, and specialist providers is necessary for optimal patient care, becoming aware of and addressing barriers affecting individuals or processes are necessary steps toward widespread prevention and early detection of metabolic disturbances.

Management of Antipsychotic-Induced Metabolic Changes

While there is no consensus on the prevention and treatment of antipsychotic-induced metabolic changes, available guidelines do outline some strategies for side effect management if metabolic changes occur. Any nonpharmacologic and pharmacologic approaches should be individualized. The 2004 ADA/APA consensus statement recommends that for patients who gain ≥5% of their initial weight at any time during treatment with an antipsychotic medication, switching to an antipsychotic medication with lower weight-gain liability should be considered.[1] If switching from one antipsychotic medication to another, one strategy is a gradual taper off of the current antipsychotic while increasing the dose of another.[1,4] The benefits and risks of a medication change should be reviewed. Examples of risks include new side effects or clinical destabilization. When possible, other medications that can cause weight gain should be avoided. Guidelines mention that treatment with a pharmacologic agent that prevents weight gain or promotes weight loss can be considered.[4,5] However, it should be noted that the evidence to support a specific change or intervention is limited, and the addition of other medications can increase costs as well as the potential for non-adherence, drug-drug interactions, or adverse events.

There is evidence to support psychosocial weight loss interventions, particularly nutritional interventions.[4,5] Providing or referring patients for at least 3 months of education on portion control, self-monitoring of caloric intake and expenditure, and goal setting for dietary and physical activity modifications can help with weight management.[46]

If a patient has or develops diabetes, hyperlipidemia, or hypertension, clinicians should assess for other contributing factors and ensure the patient receives treatment with an antihyperglycemic, lipid-lowering, or antihypertensive agent as clinically indicated.[1,4]

Summary

Patients taking antipsychotic medications are at risk for metabolic side effects that can increase the risk for morbidity and early mortality due to cardiovascular disease. Because of these combined risks, patients treated with an antipsychotic medication should be initially and routinely assessed for metabolic abnormalities, with prevention, early recognition, and treatment incorporated into the standard of care (Figure 3).

Figure 3. Prevention and management strategies for metabolic side effects of antipsychotic medications:

- Choose agents with a lower propensity to impact metabolic parameters
- Generally avoid concurrent use of ≥2 antipsychotic medications
- Routinely monitor for metabolic disturbances
- Treat metabolic abnormalities according to current guidelines
- Provide patient/caregiver education
- Establish effective communication among mental health, primary care, and other specialist providers

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