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Atypical Antipsychotics and Metabolic Abnormalities

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In Oregon, the atypical antipsychotics (AAPs) have rapidly become the mainstay of treatment for the psychopharmacotherapeutic management of schizophrenia. Currently, Oregon spends an estimated $52.5 million annually on these six drugs: olanzapine (Zyprexa), clozapine (Clozaril), risperidone (Risperdal), quetiapine (Seroquel), ziprasidone (Geodon) and aripiprazole (Abilify). The use of AAPs is not limited to schizophrenia, however, as many of the agents have been promoted to treat a number of other psychiatric diagnoses both on and off-label. Regardless of indication, the AAPs are drugs that deserve careful consideration and differentiation.

Originally, the AAPs were thought to be safer and better tolerated than the older generation neuroleptics. Traditional antipsychotics such as haloperidol (Haldol), fluphenazine (Prolixin) and thiothixene (Navane) are associated with a number of side effects. Primarily, the older agents are now avoided due to their propensity to cause extrapyramidal side effects and potentially permanent tardive dyskinesia. While AAPs cause these debilitating adverse effects to a lesser extent, certain drugs within this new class have been associated with their own unique set of problems. The adverse effects associated with a subset of the AAPs include a number of metabolic abnormalities. This article will focus on the type of metabolic abnormalities that can be associated with AAPs as well as recommended monitoring and management strategies.

In a statement released September 2003, the FDA announced that the AAPs, as a class, should include warnings of metabolic abnormalities in their package inserts. After evaluation of clinical trial data, spontaneous post-marketing reports, and other published and unpublished studies, the FDA concluded that the risk of developing diabetes mellitus in patients treated with AAPs was significant. Each manufacturer of an AAP received a letter requiring the addition of language to the *Warnings* section of the package insert regarding the risk of hyperglycemia and diabetes.[1] Newer findings, however, elevate the concern of serious metabolic abnormalities for certain drugs over others. A recent consensus statement compiled by the American Diabetes Association (ADA), American Psychiatric Association (APA), American Association of Clinical Endocrinologists, and the North American Association for the Study for Obesity, determined that clozapine and olanzapine were the two AAPs most associated with metabolic abnormalities. Based on conflicting data, no conclusions could be drawn about risperidone and quetiapine. Ziprasidone and aripiprazole were not associated with any risk of metabolic abnormalities.[2]

AAP-associated metabolic abnormalities include weight gain, alteration of blood lipids and leptin, insulin intolerance, and diabetes. In some cases, extreme hyperglycemia associated with ketoacidosis, hyperosmolar coma, or death have been reported.[3,4,5] In addition to the risk associated with drug therapy, patients with schizophrenia have been found to be more likely to have a poor diet, an inactive lifestyle, and a higher incidence of diabetes and heart disease. Data suggests that the prevalence of obesity and diabetes in patients with schizophrenia is 1.5 to 2 times higher than the general population. However, it is unknown if this finding is attributable to the disease itself or its treatment. Because risk factors for diabetes are not uncommon in patients with schizophrenia, clinicians are urged to evaluate the impact of additive metabolic adverse effects from drug therapy carefully

As previously stated, not all AAPs are equally implicated. Weight gain is commonly associated with clozapine and olanzapine, and to a lesser extent, risperidone and quetiapine. An average mean weight gain after 10 weeks of therapy has been estimated at 9 to 11 pounds with both clozapine and olanzapine. In some instances, weight gain may not reach a steady state even after a year of treatment. A comparison of AAP-associated weight gain is available in table 1.

Table 1. Metabolic abnormalities and atypical antipsychotics

Drug	Weight Gain	Worsening lipid profile	Risk for diabetes
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole	+/-	--	--
Ziprasidone	+/-	--	--

D=Discrepant results
Data from the American Diabetes Association[2]

Few published trials have examined the effect of atypical antipsychotics on *fasting* blood lipids. From the studies that are available for review, it has been shown that clozapine is associated with an increase in triglycerides, but not in cholesterol levels.[6-8] Olanzapine has been linked to both hypertriglyceridemia and hypercholesterolemia.[9,10] In one cross-sectional study, hypertriglyceridemia was found in 62% and hypercholesterolemia in 85% of patients after only seven months of therapy.[10] In contrast, risperidone and ziprasidone appear to have little to no effect on lipid levels.[11,12] Little data exist that examines this metabolic adverse effect with quetiapine and aripiprazole.

Leptin, a hormone primarily produced by adipocytes, plays an important role in body weight homeostasis and appetite. Despite the fact that the exogenous administration of leptin tends to reduce food intake and hunger, obesity in humans has been linked to high serum leptin levels and hypothalamic leptin resistance, which causes increased appetite and weight gain. Both clozapine and olanzapine seem to cause an increase in serum leptin levels, regardless of pre-treatment body weight.[11] Though fewer studies exist, the increase in leptin levels appears to be moderate with

quetiapine and minimal with risperidone. Data is currently not available to examine this effect with ziprasidone or aripiprazole.

Hyperglycemia, insulin resistance and diabetes are major concerns associated with certain AAPs. Insulin resistance can lead to both hyperlipidemia and hyperglycemia. Further, diabetes and diabetic ketoacidosis have been linked to both clozapine and olanzapine in numerous case reports. AAP-induced insulin resistance may either be primary or secondary. As a significant cause of weight gain, certain AAPs may indirectly cause insulin resistance. It is also possible that there is a direct effect. Clozapine, olanzapine, and possibly quetiapine can cause hyperinsulinemia and hyperlipidemia resulting in insulin resistance. In patients with drug-induced diabetes, a reduction in dose, or the withdrawal of therapy has been shown to improve symptoms and reverse the diabetes.[12]

Monitoring

Due to the elevated risk for metabolic abnormalities in patients with schizophrenia and those treated with certain atypical antipsychotics, the ADA and APA recommend routine monitoring. Baseline measurements obtained prior to the start of drug therapy should include: (1) personal and family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease, (2) weight and height, (3) waist circumference (at the level of the umbilicus), (4) blood pressure, (5) fasting plasma glucose, and (6) fasting lipid profile. Routine follow-up monitoring is also important. Suggested monitoring intervals are listed in Table 2.

If patients are determined to have or be at risk for diabetes, the panel recommends starting treatment with an AAP that is less likely to cause weight gain and glucose intolerance (refer to Table 1). If at any point during drug therapy the patient gains ≥5% of their initial weight, has worsening glycemia or dyslipidemia, the prescribing provider is encouraged to switch AAPs using an appropriate cross-titration method.

Summary

AAPs are commonly prescribed drugs for a variety of psychiatric diagnoses. While they are infrequently associated with extrapyramidal side effects and tardive dyskinesia, certain drugs within this class have been linked to serious metabolic abnormalities. It is now recommended that clinicians closely monitor for metabolic side effects and prescribe these agents accordingly.

Reviewed by John Muench, M.D., M.P.H. of Oregon Health & Sciences University and David Pollack, M.D., Medical Director of Office Mental Health and Addiction Services

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Table 2. Screening and monitoring for patients on AAPs

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/ family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X			X		X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

Data from the American Diabetes Association[2]

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