Concluding Discussion

Metabolic Disturbances Associated With Antipsychotic Use

Dr. Newcomer: Patients with schizophrenia may have been at increased risk for type 2 diabetes and diabetic complications before antipsychotics existed. Whether we should restrict diabetes screening only to patients taking certain medications or have different guidelines for various antipsychotics is not yet clear.

Dr. Meyer: Fasting plasma glucose and total triglyceride levels are routinely measured at baseline and annually thereafter for antipsychotic-treated patients at Oregon State Hospital. Since my colleagues and I consider the dibenzodiazepine-derived compounds (clozapine, olanzapine, and the related compound quetiapine) to be the agents of highest risk for adverse metabolic outcomes, levels are measured quarterly during the first year and semiannually thereafter in patients being treated with clozapine, olanzapine, or quetiapine. A full lipid panel is ordered when clinically indicated.

As clinicians, we're obligated to monitor patients because the psychiatrist is often the only physician a patient with schizophrenia sees. It's especially important to establish a liaison with a generalist physician who feels comfortable treating patients with schizophrenia. Weight gain is very difficult to treat in the psychiatric as well as the nonpsychiatric population. Antipsychotic-treated outpatients should be weighed at every visit and encouraged to weigh themselves between visits. Keeping a food diary is an excellent tool for a patient who begins to gain weight; the food diary will inform both the patient and physician about factors that may be contributing to weight gain. A healthy diet and enough exercise are, of course, always the best recommendations for patients who begin to gain weight, but patients need help in setting realistic short-term goals. A loss of as little as 8.5% of body weight over a year can significantly improve both glucose and lipid levels [*Rossner S, et al. Obes Res 2000;8:49–61*].

Should patients who are taking a high-risk antipsychotic have fasting glucose levels monitored more often than quarterly during the first year of treatment?

Dr. Lebovitz: We don't have enough data to know whether patients who develop ketoacidosis have an antecedent history of symptoms or acutely and abruptly develop ketoacidosis. Certainly for the routine patient, quarterly monitoring is sufficient.

Dr. Newcomer: Education is key to addressing the risk of diabetic ketoacidosis. Patients need to know to call their primary care physician if they experience abdominal pain, nausea, vomiting, depression, intercurrent illness, fever, or shortness of breath.

Dr. Lebovitz: Increased thirst and increased urination are early warning signs. When people develop polydipsia and polyuria, they often drink large amounts of sugary fruit juice or cola, adding a huge carbohydrate load, which can precipitate severe acute hyperglycemia and perhaps even ketoacidosis. Patients need to understand that they should avoid consuming large amounts of sugar-containing materials and they should see their physician if they experience polydipsia and polyuria.

Dr. Newcomer: As we consider guidelines for monitoring and treating metabolic side effects, we need to consider the finding that the number of cases of new-onset diabetes continues to climb into the fifth year of antipsychotic treatment [*Henderson DC, et al. Am J Psychiatry 2000;157: 975–981*].

Patients who are receiving maintenance antipsychotics should receive an annual screen; otherwise, the frequency of the screen is titrated to the risk in the patient. For example, an obese African American man who leads a sedentary lifestyle, smokes, is hypertensive, and has a family history of type 2 diabetes and cardiovascular disease would be monitored quarterly or more often. Taking certain antipsychotics might increase that patient's risk and thus the frequency of monitoring.

Dr. Lebovitz: What tests does your screen involve?

Dr. Newcomer: A high-risk patient might receive regular oral glucose tolerance tests. The default would be an annual fasting plasma glucose measurement.

Dr. Lebovitz: Even though a criterion for diabetes has been lowered from a fasting plasma glucose level ≥ 140 mg/dL to ≥ 126 mg/dL, as many as half the people who fail to meet this criterion meet the criterion for postprandial diabetes (≥ 200 mg/dL) [*Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1193–1197; Harris MI, et al. Diabetes Care 1997;20:1859–1862*]. If the initial screen in high-risk patients measures plasma glucose 2 hours after the ingestion of 75 g of glucose, patients might be diagnosed earlier, and the need for screening might be reduced.

Dr. Newcomer: A high-risk patient could start with an oral glucose tolerance test and be followed with regular measurements of fasting plasma glucose levels.

Dr. Lebovitz: A rise in fasting plasma glucose levels—even if they fail to reach the criterion for diabetes—indicates future problems with glucose metabolism.

Dr. Newcomer: A low-risk patient—a thin, high-activity, nonsmoker, normotensive, nondyslipidemic, white person who is being maintained on haloperidol or risperidone therapy—could be followed with an annual screen.

Dr. Lebovitz: For that kind of patient, an annual measurement of fasting plasma glucose levels would make me comfortable.

Dr. Newcomer: Dr. Henderson reported a case of diabetic ketoacidosis that evolved 4 weeks after the dose of clozapine was increased [*Am J Psychiatry 2000;157: 975–981*]. Plasma glucose levels in high-risk patients should probably be measured during the first week of antipsychotic therapy. If the level remains stable, we can feel somewhat reassured and adjust the frequency of serial measures accordingly. If the level has crept up during the first week of treatment, obviously we need to monitor the patient closely.

Dr. Lebovitz: I agree, but perhaps a baseline oral glucose tolerance test should be routine for all patients who are being started on an antipsychotic associated with a relatively high incidence of diabetes, such as clozapine or olanzapine, to rule out administering an agent with a propensity to bring out diabetes in someone with early undiagnosed diabetes.

Dr. Newcomer: Your recommendation addresses the issue of the potential impact of increased glucose levels on long-term outcomes. Even a subtle disturbance in glucose metabolism may have an impact on cardiovascular outcomes.

Dr. Meyer: Although we've discussed oral glucose tolerance tests, measuring fasting plasma glucose will identify most potential problems.

Dr. Henderson: Of the 30 patients who were diagnosed with diabetes in our study, 29 were identified after a semiannual measurement of fasting plasma glucose levels [*Henderson DC, et al. Am J Psychiatry 2000;157: 975–981*]. We need to consider the likelihood that the average psychiatrist will order regular blood tests, oral glucose tolerance tests, or 2-hour postprandial glucose measurements.

Dr. Meltzer: Can we identify a timepoint after which the increased risk of diabetes or weight gain diminishes significantly? A recommendation for quarterly monitoring in all patients who are taking these drugs may turn out to be a significant factor in discouraging the use of these agents.

Dr. Newcomer: For a low-risk patient starting treatment with a low-risk drug, such as haloperidol or risperidone, measuring a baseline fasting plasma glucose level and annual fasting glucose levels thereafter seems to constitute sufficient monitoring.

However, high-risk patients and all patients taking an antipsychotic that has been associated with metabolic disturbances, such as clozapine, olanzapine, or quetiapine, require more stringent monitoring. For these patients, the 2-hour oral glucose tolerance test should be used to measure baseline plasma glucose levels. Plasma glucose levels should be measured again after the first week of antipsychotic therapy and regularly thereafter, perhaps quarterly for the first year of treatment and semiannually after that point; the fasting glucose test can be used for these later measurements. Of course, for both low-risk and high-risk patients, monitoring should be tailored to the patient and increased when clinically indicated.

We also need to remember that the burden of prevention must remain in the psychiatrist's court. At some point, the psychiatrist will have to decide if an individual patient should continue taking an agent that may have contributed to the development of diabetes.

The advantages of atypical antipsychotic drugs are clear, but psychiatrists should weigh the risks of metabolic disturbances when selecting an atypical antipsychotic for a specific patient. Psychiatrists need to take a careful medical history, including a family medical history, and track adiposity and metabolic parameters over time. This information will help clinicians analyze the risks and benefits of a specific treatment for an individual patient.