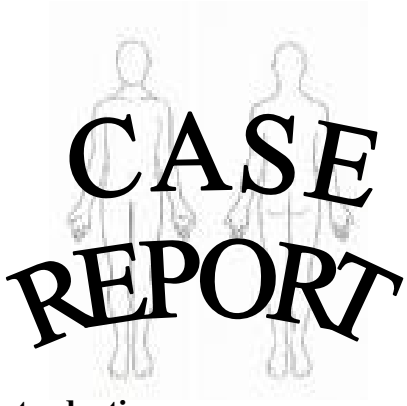

Metabolic Effect of Atypical Antipsychotics: How Bad It Can Be?

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Introduction

Metabolic syndrome has been associated with schizophrenia since long before the era of antipsychotic medications.[1] The introduction of atypical antipsychotics has been associated with worsened weight gain, hyperglycemia, and hypertriglyceridemia.[2] An American Diabetes Association/ American Psychiatric Association (ADA/ APA) consensus paper recognized that certain atypical antipsychotic medications are associated with greater metabolic dysfunction than others.[3]

A case of a young female patient with uncontrolled type 2 diabetes mellitus on atypical antipsychotics is presented. Her antipsychotic medications were discontinued due to pregnancy. The patient subsequently had significant weight loss and improvement in her glycemic control.

Case Report

A 35-year-old female was seen in the endocrinology clinic for type 2 diabetes mellitus complicated by gastroparesis, peripheral neuropathy, and nephropathy. Glycemic control had not been achieved on insulin glargine 40 units twice daily, insulin lispro 10 units before meals, pioglitazone 30 mg daily, and metformin 850 mg twice daily. Hemoglobin A_{1c} was thirteen percent.

Her past medical history was significant for resolved renal failure secondary to lithium toxicity, asthma, primary hypothyroidism, bipolar disorder, hyperlipidemia, hypertension, and schizophrenia. Other medications included quetiapine 500 mg daily in a divided dose, citalopram 40 mg daily, divalproex 2500 mg daily, aripiprazole 20 mg daily, levothyroxine 100 mcg daily, lisinopril, pravastatin, pantoprazole, docusate, aspirin, propranolol, odansetron, promethazine, metoclopramide, and trazodone.

Physical exam revealed a blood pressure of 113/69 mmHg, weight 99.5 kg, a body mass index (BMI) of 35 kg/m^2, mild acanthosis nigricans, and decreased sensation in both feet. Cushingoid features were not present. Urine free cortisol in a 24-hour collection was not elevated.

Metformin was discontinued because of diarrhea. The patient attended diabetic education sessions and attempted dosing insulin by carbohydrate counting without success. The pharmacy confirmed that her prescriptions were being filled and she was observed taking insulin in clinic with little demonstrable effect on her blood glucose.

She became pregnant and all medications were discontinued with the exception of insulin, levothyroxine, and citalopram. Acceptable glycemic control was achieved on insulin glargine 50 units once daily and insulin aspart 27 units three times daily.

Term delivery was complicated by failure to progress, resulting in a Cesarean section. The infant was not macrosomic. The patient experienced postpartum respiratory failure of uncertain etiology requiring brief mechanical ventilation. Marked hypoglycemia occurred post-partum

and insulin was discontinued.

She was seen in the endocrinology clinic seven weeks post-partum without diabetic or antipsychotic medications. Her hemoglobin A_{1c} was 6.5 percent and her weight had decreased to 81.87 kilograms. She was not breastfeeding. She was restarted on metformin 1 gram twice daily and later extended release glipizide 5 mg daily. Subsequent follow-up showed well controlled blood glucose and stable weight.

Discussion

Schizophrenia has a prevalence of 1%.[4] It is associated with a significant increase in mortality. A correlation between diabetes mellitus and schizophrenia has been observed for many years. In 1879, Sir Henry Maudsley wrote, "Diabetes is a disease which often shows in families in which insanity prevails."[5] The prevalence of type 2 diabetes mellitus in patients with schizophrenia is 9% versus 4.6% in the general population.[6]

The reasons that underlie the high prevalence abnormalities are much debated.[7] In spite of the increased risk of metabolic disturbances, patients with severe mental illness are less likely to receive treatment for hyperlipidemia, hypertension, or diabetes mellitus than patients without psychosis.[8]

Pharmacologic agents used in the treatment of schizophrenia, particularly second generation antipsychotics, have been linked to the metabolic syndrome. The US Food and Drug Administration has labeled this as a class effect, although there are major differences in risk associated with the various medications.[9]

Clozapine causes metabolic syndrome in more than 50% of long time users.[10] The risk of new-onset diabetes was equivalent for patients treated for one year with olanzapine, risperidone, or quetiapine, and significantly greater than in patients treated with haloperidol.[11] Atypical antipsychotics also have been associated with a small increase in risk of diabetic ketoacidosis.[12] In a case control study comparing patients treated with antipsychotic drugs to control patients without antipsychotic medication, the odds ratio for hyperlipidemia ranged from 1.82 for clozapine to 1.26 for first generation antipsychotics; aripiprazole was the only antipsychotic that did not increase the risk for hyperlipidemia significantly.[13]

Several mechanisms have been proposed to explain the effect of antipsychotic medications on the metabolic syndrome. Antipsychotics can disrupt energy balance, creating an imbalance between energy intake and expenditure, thus resulting in weight gain and obesity.[14] This can be explained partially by antagonism of histamine and possibly by serotonin inducing weight gain, which in turn leads to changes in glucose homeostasis.[15] Some antipsychotic drugs may have direct inhibitory effects on insulin release from pancreatic beta cells.[16] Other theories include a potential direct blockade of glucose accumulation at the level of the glucose transporter in cells derived from both peripheral and brain tissue,[17] perturbation in appetite regulation, and the release of counter regulatory hormones.[18]

Treatment. No adjunctive medication has been conclusively shown to reduce these metabolic effects.[19] Even among drugs showing positive effects for preventing weight gain, such as metformin, the metabolic effects have been modest. Patients who develop antipsychotic-induced metabolic disturbance should be switched, if clinically practical, to an agent with fewer propensities for this side effect, such as aripiprazole or ziprasidone. A consensus statement prepared by the American Psychiatric Association, the American Diabetes Association, and others recommended baseline assessment of weight, blood pressure, fasting plasma

glucose, and fasting lipid profile, and reassessment 12 weeks after initiation of the antipsychotic medication.[3] Patients with impaired fasting glucose should be tested for diabetes with a two-hour oral glucose tolerance test. Weight should be followed monthly for the first three months and quarterly thereafter.

Conclusion

The association between schizophrenia and the metabolic syndrome has long been recognized. Unfortunately, metabolic disturbances, including diabetes mellitus, hypertension, hyperlipidemia, and weight gain, appear to be caused or exacerbated by atypical antipsychotics. Several mechanisms have been proposed, mainly a perturbation of the body's ability to react, metabolize, and transport glucose causing weight gain and exacerbating insulin resistance. Patients requiring antipsychotic medications should be assessed for aspects of the metabolic syndrome before and during treatment. Switching to antipsychotic medications not related to metabolic disturbances or even discontinuing antipsychotic medications should be evaluated on an individual patient basis.

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