Case Report: Lack of Control of Diabetes and Weight Gain in a Patient on Initiation and Rechallenge of Therapy With Olanzapine

Summary
The following is a case report analysis intended to draw attention to the need for better care coordination by describing the observed relationship of olanzapine to metabolic changes manifested as uncontrolled diabetes mellitus and weight gain. A 47-year-old male with bipolar I disorder/hallucinations presented to the Veterans Affairs Medical Center (VAMC) with suicidal ideations. He was referred to the psychiatry service where he was treated with olanzapine. He was followed exclusively by the psychiatry service for more than a year. During that time, weight issues and diabetes status were not addressed. Upon presenting to the primary care service a year and a half later, the patient was taking 40 mg per day of olanzapine and had gained 62 pounds, a 30% increase in body weight; glycosylated hemoglobin (A1c) was 11.1%. The patient was enrolled in a weight-loss clinic, and his diabetes medications were adjusted. Subsequently, olanzapine was discontinued because of weight gain and uncontrolled diabetes. Blood sugar and A1c were finally stabilized one month after discontinuation of olanzapine (A1c, 6.9%). The patient experienced a relapse in his bipolar disorder, and olanzapine was restarted at 20 to 40 mg per day. His blood sugar became uncontrolled, he gained 13 pounds, and his A1c increased to 9.4%.

Background
Atypical antipsychotics were developed in order to decrease side effects that are associated with first-generation antipsychotics. While the atypical antipsychotics have fewer or no extrapyramidal side effects, they have been associated with metabolic changes, such as glucose dysregulation and weight gain. All atypical antipsychotics have the potential to cause these changes, but clozapine and olanzapine appear to have the highest risk. In March 2004, at the request of the U.S. Food and Drug Administration, a section detailing the link between atypical antipsychotics and hyperglycemia and diabetes mellitus was added to the olanzapine package insert, as well as to the inserts of all other atypical antipsychotics. This new warning states that “patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.” The Consensus Statement developed by the American Diabetes Association (ADA) and the American Psychiatric Association (APA) outlines a more specific approach. Monitoring of blood glucose is recommended at baseline, 12 weeks, and annually, while measurement of body mass index is recommended at baseline, 4 weeks, 8 weeks, 12 weeks, quarterly, and annually. It is also recommended that patients who gain >5% of their initial weight should consider switching to an alternate agent.

Olanzapine is an atypical antipsychotic currently indicated for the treatment of schizophrenia and bipolar disorder. The mechanism of action is unclear, but it has binding affinity for serotonin 5HT2A/2C, dopamine D1-4, muscarinic M1-5, histamine H1, and alpha1-adrenergic receptors. The typical dose ranges from 5 to 20 mg daily. The first reported case of olanzapine-induced hyperglycemia dates back to 1998. Since that time, olanzapine’s potential to cause hyperglycemia as well as weight gain has been established; however, the frequency or severity of these reactions is still undetermined.

The VAMC is a managed care organization that utilizes a national drug formulary. There are approximately 150 VAMCs in the United States. Because of the large number, VAMCs are categorized into Veterans Integrated Service Networks (VISNs). There are 22 VISNs in the United States. Each VISN has the ability to review, vote on, and add certain medications to their formulary that might not currently be on the national formulary. Treatment options are monitored through computerized records (i.e., medication refill history; appointment schedules; and lab values, such as A1c). All VAMC patient records are computerized, which allows practitioners to have access to all medical notes, including primary care and sub-specialties. VAMC also allows the dissemination of information on treatment guidelines or clinical pathways to practitioners.

Despite provider education on the recommendations from the ADA and APA, providers do not always take an active role in monitoring their patients. Because of this, uncontrolled disease states caused by atypical antipsychotics may lead to patient nonadherence as well as higher health care costs pertaining to negative outcomes from new disease states. The following case details the hyperglycemic events and weight gain issues associated with olanzapine therapy not only on initiation but also upon rechallenge. It also emphasizes the need for continuous monitoring and care coordination among providers.

Case Report
A 47-year-old white male presented for his first visit to the outpatient primary care clinic on February 27, 2002. His past medical history was significant for type 2 diabetes (unknown date of diagnosis), osteoarthritis, bipolar I disorder/hallucinations, and alcohol abuse (abstinent since 1991). His medications prior to this visit were depakote, clonazepam, olanzapine, glipizide XL, and metformin (doses and frequencies unknown). The patient’s weight at initial visit was 208 pounds. His diabetes status and blood work were not evaluated at this visit because the patient expressed suicidal ideations and was referred to the psychiatric emergency clinic.

He was to come back within a week to get his blood drawn, but he did not follow through. He did come in 3 months later and had a fasting blood sugar of 144 mg/dL. His psychiatric disorder was followed closely by the mental health clinic for the next year, but his diabetes status and weight were not addressed during this time frame. He was initially prescribed olanzapine
5 mg four times a day, and, over the course of 6 months, his dose was titrated up to 40 mg in the evening. The chart stated no reason why this starting dose was used or why it was increased to above the maximum recommended dose.

Six months after the dose was increased to 40 mg in the evening, the patient presented to the mental health clinic with his wife, who requested that his medications be decreased because of his weight gain (weight measured at home was 268 pounds). The patient and his wife stated that eating habits had not changed at home. The olanzapine dose was decreased to 20 mg in the evening.

On September 23, 2003, the patient was seen by his primary care provider (about a year and a half after the initial primary care visit). There is no explanation as to why there were no prior primary care visits. At that visit, the patient’s weight was 270 pounds and A1c was 11.1%. His medications for diabetes at that time were glipizide XL 10 mg/day, metformin 500 mg twice a day, and pioglitazone 30 mg/day. His medications were adjusted and converted to formulary agents (metformin 1 gram twice a day and glipizide 10 mg twice a day; he continued receiving pioglitazone from an outside provider because it was nonformulary, and he did not meet criteria to obtain it from our health system). He was checking his blood sugars at home, but there is no record of what those readings were at this visit. He was given and taught to use a glucometer (Precision) because this facility has the ability to download data from this glucometer to determine blood sugar averages, ranges, and percentages below goal (<80 mg/dL), within goal (80-140 mg/dL), or above goal (>140 mg/dL). He was enrolled in a weight-loss clinic.

On March 11, 2004, the patient’s A1c was 10.3%, and insulin human isophane (NPH) 10 units every evening was initiated. He had stopped taking the pioglitazone because he was no longer seeing a physician outside of the VAMC. At that time, he was referred to a clinical pharmacy clinic. He was seen on a regular basis to download data from his glucometer, titrate his diabetes medications, and check his weight.

On March 24, 2004, his glucometer data from the previous 2 weeks showed an average blood sugar of 296 mg/dL, with a range from 195 to 413 mg/dL (20 readings; 100% above goal). His weight was 269 pounds, and his NPH insulin was increased to 20 units every morning and 10 units every evening.

On April 21, 2004, his blood sugar average for the previous 2 weeks was 291 mg/dL, with a range from 213 to 420 mg/dL (49 readings; 100% above goal). His insulin was changed to 70/30 insulin 20 units in the morning and 10 units in the evening.

Over the course of the next 3 months, his insulin dose was titrated to a dose of 85 units in the morning and 75 units in the evening, and there were no changes in his oral antidiabetic agents.

On July 27, 2004, his A1c was 9.4% and his weight was 262 pounds. His glucometer data showed an average blood sugar of 187 mg/dL with a range from 83 to 328 mg/dL (unknown number of readings; 27% within goal and 73% above goal).

On August 25, 2004, the patient saw his psychiatrist and requested that his olanzapine be discontinued because of his weight gain and his inability to lose the weight. The olanzapine was tapered as follows: 10 mg every evening for 2 weeks, then 5 mg every evening for 2 weeks, and then stopped. His mental health care provider did not initiate another antipsychotic to replace olanzapine even though the patient’s note stated that he was reluctant to stop the olanzapine because he was “doing so well on it.”

He was then seen in the primary care clinic on October 21, 2004, one month after discontinuing his olanzapine. During this time, his blood sugars dropped significantly. His average for the previous 2 weeks was 114 mg/dL, with a range from 53 to 185 mg/dL (19 readings; 21% below goal, 47% within goal, 32% above goal). His insulin was decreased to 80 units in the morning and 70 units in the evening. During that same time, the patient saw his psychiatrist and requested that olanzapine be restarted because he was hearing voices. Olanzapine was restarted at 20 to 40 mg every evening (he was taking 40 mg). There is no reason stated as to why a dose of 20 to 40 mg was chosen, since the 40 mg dose is again above the recommended maximum dose.

On November 3, 2004, his blood sugar average was 209 mg/dL with a range of 174 to 283 mg/dL (unknown number of readings, 100% above goal). His insulin 70/30 was increased back to 85 units in the morning and 75 units in the evening.

Two weeks later, he presented to the clinic with a blood sugar average of 262 mg/dL and a range of 202 to 340 mg/dL (11 readings, 100% above goal). Insulin was increased to 95 units in the morning and 85 units in the evening.

He returned in January 2005 and weighed 281 pounds and had an A1c of 9.4%. His mental health care provider kept him on olanzapine and never addressed the issue of weight gain again.

Discussion

Koller and colleagues reviewed cases of hyperglycemia associated with olanzapine from the Med Watch Drug Surveillance System. The time of onset of hyperglycemia ranged from 2 days to 45 months, with the majority occurring at 6 months or fewer. They also discovered that, while the onset of hyperglycemia may have been rapid and severe, the association was not dose dependent.

The reason for hyperglycemia associated with the use of olanzapine is not clear. While weight gain may play a role, other causalities likely exist. There are several theories about how olanzapine can induce hyperglycemia. One theory postulates that serotonin (5HT1A) antagonism has the ability to cause low insulin secretion by blunting the response of the pancreatic beta cells. Other theories include a dysregulation of the sympathetic system and insulin resistance due to alteration of the receptor-binding characteristics. Lastly, it has been hypothesized that atypical antipsychotics may decrease the half-life of glucose transporters. Therefore, there are fewer transporters to carry glucose. The mechanism of action...
for this theory is unknown.

This case deals with the hyperglycemia apparently caused by olanzapine therapy, the resultant decrease in glucose levels when the agent was discontinued, and the subsequent hyperglycemia when the agent was rechallenged. Literature shows that the time to return to baseline glucose levels varies after olanzapine has been discontinued and that some patients do not return to baseline at all.\textsuperscript{2,4,6-7} Koller's study showed that 8 out of 10 patients had worsening of their glycemic control upon rechallenge with olanzapine.\textsuperscript{7}

Worsening of glucose control upon rechallenge was also apparent with this patient. He demonstrated hyperglycemia, with a significant weight gain (approximately 37\% of initial body weight). The ability of olanzapine, to cause weight gain is well documented.\textsuperscript{2,8,10,11} Medications that antagonize serotonergic transmission, such as olanzapine, may cause an increase in food consumption. The amount of weight gain correlates with the agents' affinity for H\textsubscript{1} receptors. Also, the sedative effects of atypical antipsychotics can lead to a sedentary lifestyle, thus contributing to weight gain.\textsuperscript{1,6,12}

There is literature to support the idea that weight gain may be minimized with nutritional intervention.\textsuperscript{13} This patient did attend weight-control classes but was unable to reverse the weight gain. Also, a case report found that by improving negative symptoms in a patient with schizophrenia, weight gain was minimized because she became motivated to diet and exercise regularly.\textsuperscript{14}

As with most retrospective case reports, not all pertinent information was available about our patient. For example, a baseline A1c was not obtained, and there was no explanation as to why doses exceeding the recommended maximum dose were used. He was also lost to follow-up in the primary care clinic for more than one year. During this time frame, the patient was being closely evaluated for his bipolar disorder in the mental health clinic. While the mental health care provider evaluated the efficacy of the olanzapine, he never addressed or evaluated the possible side effects (such as weight gain and glucose deregulation) during the course of treatment.

Records at this facility are computerized, thereby allowing practitioners to view all notes from patients' visits. The mental health care provider was able to see that the patient had not had a primary care follow-up appointment for more than a year. While diabetes status and weight issues are usually addressed by a primary care provider, these issues should also have been addressed by the patient's mental health care provider.

DISCLOSURES
The author discloses no potential bias or conflict of interest relating to this article.

REFERENCES