



## Atypical Antipsychotics and Diabetes Mellitus: An Association

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The atypical antipsychotic agents, e.g., clozapine, olanzapine, risperidone and the more recent ones quetiapine, ziprasidone and aripiprazole, have become the preferred treatment for schizophrenia and schizoaffective disorders. They offer significant advantages over older antipsychotic agents, such as haloperidol, including a marked reduction of drug-induced extrapyramidal symptoms and risk for tardive dyskinesia [1,2]. However, these drugs are associated with significant side effects such as weight gain, disturbance of lipid metabolism, impaired glucose tolerance and type 2 diabetes mellitus, which are associated with a significantly increased risk of cardiovascular morbidity and mortality, as well as acute dysregulation of glucose metabolism presenting as diabetic ketoacidosis. On the other hand, there is also a known association between schizophrenia and diabetes mellitus independent of psychotropic drug use [3,4]. Moreover, poorly controlled diabetes mellitus may worsen tardive dyskinesia [5].

### Epidemiology

For many decades, even before the introduction of antipsychotic medications, studies suggested that impaired glucose metabolism is more common among patients with schizophrenia than in the general population (6% and 1% respectively) [6]. A recent Italian study of 95 schizophrenic patients found that the prevalence of diabetes was 15.8%, independent of the treatment used, compared with the 3% in the general Italian population [3]. A study of diabetes prevalence in different types of psychiatric disorders showed that 50% of patients with schizoaffective disorders, 26% of bipolar I patients and 18% of patients with other psychiatric disorders had diabetes [2]. These findings were independent of age, race, gender, body mass, and type of medication used. Over the past few years several clinical observations have suggested an association between the use of atypical antipsychotics and the onset of new diabetes mellitus or worsening of existing diabetes. The association persists even after adjustment for relevant risk factors. Of the few large population studies conducted to confirm this association [7–9], most showed that the use of atypical antipsychotics, including olanzapine and clozapine but not risperidone, incurs a greater risk for the development of diabetes than conventional antipsychotic treatment.

Lean and Pajonk [10] summarized all cases reported up to January 2002 and concluded that the overall risk was highest for clozapine and slightly less for olanzapine. Risperidone and conventional antipsychotics had the same overall risk. Koller and co-workers [11,12], on the other hand, examined the clinical characteristics of patients who developed hyperglycemia during treatment with the various atypical drugs and found that although the cases attributed to clozapine and olanzapine were more numerous than those associated with risperidone, the number of risperidone-associated patients with hyperglycemia was relatively higher than the number of those treated with haloperidol. In a few case reports quetiapine therapy was also shown to be associated with diabetes. The very latest drugs introduced in the last 2 years, ziprasidone and aripiprazole, have not been reported to cause hyperglycemia [10]. Koro et al. [13] quantified the association between olanzapine and diabetes in a population-based nested case-control study. After adjustment for personal risk factors and concomitant drug use, the incidence of diabetes in patients taking conventional or newer antipsychotics was 4.4/1,000. Women exhibited a higher incidence than men (5.3 vs. 3.5/1,000 person-years) in this specific study. The incidence was significantly higher with olanzapine (10/1,000) but not with other newer antipsychotics such as risperidone (5.4/1,000). Several studies [10,14,15] demonstrate an age-related risk for diabetes only in patients on atypical antipsychotics (compared to conventional treatment). In one study the increased risk was found in patients under the age of 60 [14], and in another in patients aged 20–34 [15]. No significantly increased risk was shown for older patients.

In contrast to these studies, others [16] showing an increased risk of diabetes with the use of antipsychotics did not find any difference between conventional and atypical agents. These results are conflicting. One prospective randomized, but not placebo-controlled study [17] followed 101 schizophrenic or schizoaffective patients receiving clozapine, olanzapine, risperidone or haloperidol for 14 weeks. Fasting glucose and cholesterol levels were recorded. There was a significant increase in glucose levels of patients taking clozapine, olanzapine and haloperidol, but in most of them the values remained within the normal range. Only 14% of the patients had abnormally high glucose levels. Risperidone therapy was

associated least with diabetes. The limitation of this study was the rather short follow-up, since in many instances the development of diabetes occurs many months after the initiation of antipsychotic therapy. In addition, this study examined only glucose and cholesterol and therefore was unable to contribute to elucidating the nature or the mechanisms underlying the association. Another study [18] compared oral glucose tolerance tests in 48 schizophrenic patients receiving clozapine, olanzapine, risperidone or typical antipsychotics to test results of untreated healthy controls matched for age and body mass index. The patients were on medications from 19 days to over 1 year prior to testing. Here too, clozapine and olanzapine but not risperidone or typical antipsychotics were associated with impaired plasma glucose regulation that varied in severity but was independent of adiposity and age. To our knowledge, no large prospective study with a long-term follow-up has been published.

### Clinical manifestations

The clinical manifestations of diabetes induced by atypical antipsychotics are based only on case reports. The average duration of exposure to the drugs prior to the detection of diabetes was 17–18 weeks, ranging from a few days to several years [19]. Koller et al. [11,12] found that most of the patients (73% for olanzapine and 68% for risperidone) developed diabetes in less than 6 months. In most reports [5,19], men had a greater risk of developing diabetes than women, and African Americans were more prone than other ethnic groups. Koller and associates [11,12] reported a male:female ratio of 1.8 for olanzapine and 1.5 for risperidone. Many case reports note a significant weight gain with the use of antipsychotic drugs prior to the development of diabetes and imply that diabetes develops as a consequence. In contrast, Meyer [20], who performed a retrospective study reviewing charts and comparing the metabolic outcomes of 76 patients who received olanzapine and risperidone, found a significant increase in fasting blood glucose levels in patients treated with olanzapine, which was not correlated with changes in weight.

In contrast to the insidious onset of type 2 diabetes, diabetic ketoacidosis has been reported as a dramatic presentation of atypical antipsychotic-induced diabetes [21]. Ananth et al. [19] reviewed all case reports of patients treated with olanzapine and clozapine who developed diabetes, and found that 35% presented with diabetic ketoacidosis. Lean and Pajonk [10] found similar results. Jin and colleagues [22] analyzed 45 published cases of new-onset antipsychotic-induced diabetes; 19 patients (42%) who presented with DKA were significantly younger, more often female and less overweight at baseline than patients who developed diabetes without ketoacidosis. No differences in ethnicity, weight gain, family history of diabetes, or duration of exposure to antipsychotic drugs were found. Many of the patients who were diagnosed with new-onset diabetes, including patients presenting with DKA, recovered completely after changing the antipsychotic drug [22]. In others, it was necessary to continue antiglycemic therapy, mostly insulin and metformin, despite the overall

improvement after changing the antipsychotic treatment, in order to maintain metabolic control. In most patients for whom it was necessary to continue the atypical antipsychotics, control was achieved with oral antiglycemic drugs. Patients restarted on the same antipsychotic drug became hyperglycemic again.

### Mechanism of action

The mechanism by which atypical antipsychotic drugs cause diabetes and other metabolic disturbances is not fully understood, mainly because schizophrenia itself plays a role in the development of diabetes. Since most patients receive multiple antipsychotic drugs, it is difficult to identify the effect of each single medication.

Excessive weight gain, observed with various antipsychotic drugs and especially with atypical antipsychotics, is one of the explanations offered [19,24,25]. There are several factors that influence weight gain and they differ for each drug; one of them is the antagonism of the serotonin receptor. Weight gain causes insulin resistance and, as a result, the other components of the metabolic syndrome. However, there are reports [26] of patients who developed diabetes without prior weight gain. Moreover, once the drug is withdrawn the glucose level improves promptly before weight loss is apparent.

Yazici et al. [27] studied levels of glucose, insulin and C-peptide during OGTT in patients before and after a 6 week treatment course of clozapine. They found that clozapine increased all of these measures. Newcomer et al. [18] compared glucose tolerance tests in 48 patients treated with various antipsychotics with the results in healthy controls. Only patients on olanzapine showed an increase in HOMA IR (Homeostasis Model Assessment of Insulin Resistance) values.

Leptin is a hormone synthesized by adipocytes. It is important in controlling body weight. Plasma leptin is correlated with fat mass and insulin resistance. Hagg et al. [28] found that plasma leptin concentration was elevated independently of weight in patients treated with clozapine.

Glucose transport was shown to be inhibited by some antipsychotics [29]. This effect was shown in PC12 cells in culture that represents a model of neuronal differentiation *in vitro* and in L-cells representing skeletal muscle. Ardizzone et al. [29] found a correlation between the ability of a drug to inhibit glucose transport *in vitro* and its ability to induce hyperglycemia *in vivo*.

These observations suggest that insulin resistance might be responsible for the development of diabetes following treatment with atypical antipsychotics, but it may not be the only factor because the rapid development of diabetes in many of these patients suggests a direct and possibly toxic effect of the antipsychotics.

The dopamine and the serotonin systems are believed to play a major role in the antipsychotic action of the atypical neuroleptic drugs. Receptors for both these neurotransmitters have been shown to play a prominent role in inducing diabetes. Chlorpromazine, a typical antipsychotic, blocks the D2 receptor and is known to cause

DKA = diabetic ketoacidosis

OGTT = oral glucose tolerance test

diabetes [5,30–32]. Bromocriptine, a dopamine agonist, reverses hyperglycemia. Blocking of D2 receptors leads to an increase in neurotensin, which is responsible for both the antipsychotic as well as the diabetogenic effects of these drugs.

Atypical antipsychotics, which block both dopaminergic and serotonin receptors, produce diabetes more often than neuroleptics, which block only dopamine receptors [33,34], thus emphasizing the importance of serotonergic receptors. It has been shown that knockout of the 5-HT2C receptor in mice can produce weight gain. Reynolds and associates [35] identified a genetic factor, -759C/T polymorphism of the 5-HT2C receptor regulatory region, that associates weight gain and antipsychotic treatment in humans. However, the exact role of these receptors, and the mechanisms by which they induce diabetes warrant further investigation.

Acute pancreatitis is another effect known to be associated with the use of atypical antipsychotics. Koller and team [36] investigated this association and found that pancreatitis is reported more frequently for clozapine, followed by olanzapine, and then risperidone. In addition, there are case reports of atypical antipsychotic-induced DKA associated with the development of pancreatitis [37]. The association of antipsychotic-induced pancreatitis with diabetes has been attributed to immediate damage to the pancreas, but Koller et al. did not find a direct connection. Some patients developed diabetes before the development of pancreatitis, and since many of the patients with diabetes have high insulin rather than the low insulin level expected from pancreatitis, this connection is not unequivocal.

The mechanism underlying the development of ketoacidosis, which is typical of type 1 diabetes mellitus and implies severe insulin deficiency, is not quite understood. Nevertheless, a direct inhibitory effect on beta cells seems to be involved. Reports of patients on atypical antipsychotic drugs who presented with DKA lack substantial information that could be of help in understanding this relationship. One study [24] that reported three cases of DKA found that C-peptide, examined on admission in two patients while still on the antipsychotic drug, was 0.7 and 0.9 nmol/L. One month after withdrawal of the drug, C-peptide rose to 0.9 and 1.6 nmol/L respectively, suggesting a temporary deficiency of insulin. In all case reports where antipancreatic antibodies were examined they were found to be negative.

These findings, together with the fact that in most patients diabetes is reversible, suggest that there is some sort of primary transitory damage to the pancreas. A study that investigated the influence of antipsychotic drugs on insulin release from pancreatic beta cells *in vitro* [38] found that clozapine increases insulin release and haloperidol (a conventional antipsychotic) inhibits the glucose-stimulated release of insulin, but other antipsychotics had no effect on insulin release. Sowell et al. [39] studied the effect of olanzapine and risperidone on beta-cell function in healthy volunteers. Insulin secretion was assessed at baseline and at the end of treatment with the different drugs, using the hyperglycemic clamp technique. This study found no evidence that these drugs decrease insulin secretory response to a prolonged hyperglycemic challenge. Ketoacidosis in response to

atypical antipsychotics still remains a puzzle and much has yet to be elucidated regarding the role of these drugs and the mechanisms by which they induce diabetes.

### Summary and conclusions

The use of atypical antipsychotic agents is associated with the induction of both an indolent progression to insulin-resistant diabetes and an idiosyncratic beta-cell toxicity presenting as diabetic ketoacidosis, both of which are usually reversible or improved subsequent to cessation of treatment. The underlying mechanisms are unclear at present. Nonetheless, in light of the now numerous reports on the adverse metabolic effects of these drugs, the Consensus Development Conference which met in November 2003 [40] recommends that metabolic risks be considered when starting atypical antipsychotic drugs. Their operative checklist includes baseline screening of candidates for antipsychotic treatment, which includes personal/family history of diabetes, weight, waist circumference, blood pressure, fasting plasma glucose and fasting lipid profile, and then follow-up of these parameters. Furthermore, the health professionals, patients, family and caregivers should be aware of the signs and symptoms of diabetes, especially when acute decompensation occurs which is commensurate with diabetic ketoacidosis.

We wish, through this short report, to raise the awareness of physicians treating psychiatric patients to the possibility of new-onset diabetes during therapy with atypical antipsychotic drugs and to emphasize the necessity for increased vigilance and close metabolic follow-up of these patients. Moreover, the choice of the best antipsychotic treatment for each patient should take into consideration the diabetogenic effect of the different treatment options as well the other side effects.

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