Disturbances of Glucose and Lipid Metabolism During Treatment With New Generation Antipsychotics

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Abstract and Introduction

Abstract

Purpose of Review: The purpose of this paper is to review the recent literature about alterations of lipid and glucose metabolism in patients treated with second generation antipsychotics. This article also addresses possible underlying mechanisms of these changes and discusses ways of preventing these side-effects as well as their management.

Recent Findings: There is a considerable number of reports on this issue but very few prospective controlled trials dealing with this very important subject. This review further focuses on the question of whether there is a difference with respect to such alterations between the available new generation antipsychotics, depending on their receptor profiles.

Summary: As adverse metabolic effects have a high impact on the physical health of schizophrenia patients as well as on their treatment adherence, this is a topic of major clinical relevance, with implications for public health.

Introduction

Several mechanisms have been discussed to be involved in antipsychotic-induced glucose dysregulation: the role of 5HT-antagonism, for instance, remains controversial, as 5HT1 and 5-HT2A serotonin receptors may have opposite effects on glucose homeostasis.[1,2] The best-understood risk factor is the development of antipsychotic-induced obesity.[3] Weight gain under antipsychotic treatment is thought to be the result of antihistaminergic and antiserotonergic effects.[4] Another factor potentially of relevance is beta-cell toxicity, which has been found in animal studies and in several patients who had developed ketoacidosis during antipsychotic treatment.[5] Furthermore, it has been hypothesized that antipsychotics could lead to insulin resistance by directly affecting insulin signalling in muscle cells.[6] A role of prolactin in the dysregulation of glucose metabolism has also been suggested.[6] Prolactin has been found to be elevated during treatment with antidopaminergic drugs[7] and this has been linked to lower insulin sensitivity, subsequently leading to insulin resistance.[8] In summary, the mechanisms causing insulin resistance remain unclear and may occur at any step of the signalling pathway, including alterations in insulin receptor kinetics and intracellular signal processing.[6]

Insulin resistance leads to an increased production of insulin in pancreatic beta cells. If pancreatic function is intact and the compensatory activation of beta cells leads to the production of sufficient amounts of insulin, manifest alterations of glucose metabolism are unlikely. If, on the other hand, beta-cell function is impaired, overt diabetes could be the consequence. Another result of an alteration of beta-cell activity is a disarrangement in the processing of proinsulin to biologically active insulin which has been found to precede the onset of overt hyperglycemia.[5]

The mechanisms causing hyperlipidemia are even less clear. The most likely one is weight gain.[9] Further hypotheses related to dietary changes, as well as to glucose intolerance causing secondary hypertriglyceridemia.[9]
In this manuscript, we review the current literature in respect to metabolic alterations caused by second generation antipsychotics. Furthermore, we include an analysis of the available data and recommendations for the prevention and treatment of these alterations, as alterations of both glucose metabolism and lipid metabolism are major risk factors for cardiovascular events and are therefore highly clinically relevant.

**Alterations of Glucose Metabolism During Treatment With New Generation Antipsychotics**

Alterations of glucose metabolism have been reported during treatment with the following new generation antipsychotics.

**Clozapine**

Several cases of clozapine-induced alterations of glucose metabolism have been reported in the last few years. Henderson et al., who investigated 101 patients treated with clozapine, were the first to study the potential diabetogenic effect of clozapine in a larger sample. Of those patients, 19 developed diabetes mellitus. Some more recent investigations have reported cases of diabetic ketoacidosis during treatment with clozapine.

Melkersson et al., compared patients treated with clozapine to a group treated with conventional antipsychotics and found signs of insulin resistance in patients on clozapine. Insulin levels were positively correlated with clozapine serum levels. Another study investigated clozapine and haloperidol-treated patients using a glucose tolerance test. These authors found impaired glucose tolerance in patients treated with clozapine and no glucose metabolism changes in haloperidol patients after eight weeks of treatment. Avram et al. studied patients that had developed ketoacidosis during treatment with clozapine using patch clamp assessment - a method to measure beta-cell function - and found alterations of beta-cell function. Fernandez et al. investigated patients suffering from Parkinson's disease who were treated with clozapine. The prevalence of diabetes in this cohort of 44 patients was 18.1%, which is similar to the rate reported in the age-matched general population. Next to these studies, around 30 case reports about clozapine-induced diabetes or ketoacidosis have been published. Interestingly, Lu et al. found an inhibition of clozapine-induced weight gain and alterations of serum glucose triglyceride and cholesterol levels when adding fluvoxamine to clozapine. Further studies are badly needed, especially with regard to clozapine-induced metabolic disturbances. Although there are some indications that alterations of beta-cell function in the pancreas may play a role, there is, as yet, no definitive proof for this.

**Olanzapine**

Hyperproinsulinemia, a sign of insulin resistance, has been found in a cross-sectional study in 14 patients over a 6-month treatment period with olanzapine. Three of these patients had signs of manifest diabetes. Another study conducted by Melkersson in 2003 also found hyperproinsulinemia after a mean olanzapine exposure of 25 months. Lindenmayer et al. investigated 47 patients treated with olanzapine and found intermittent or persistent hyperglycemia. Insulin levels were not measured in this study. Several groups investigated potential beta-cell toxicity caused by olanzapine. Sowell et al. did not find any signs of beta-cell dysfunction using a patch clamp assessment in healthy volunteers who had received olanzapine for a duration of 14-17 days. Ebenbichler et al. also failed to find signs of beta-cell alteration in an 8-week prospective investigation.

Around 50 case reports about olanzapine-induced diabetes or ketoacidosis have been published, including a recent one in which three patients on olanzapine who died unexpectedly following diabetic ketoacidosis were described.

**Quetiapine**

Quetiapine is not sufficiently investigated with respect to metabolic side-effects. In addition to reporting 46 cases, ranging from mild hyperglycemia to diabetic ketoacidosis linked to treatment with quetiapine, Reinstein et al. have investigated changes in body weight and diabetes status in patients treated with clozapine combined with quetiapine in a nonrandomized retrospective study. Before being treated with this combination, patients had received clozapine monotherapy. Combination treatment resulted in a significant reduction in body weight, as well as in glucose levels (in 20% of the patients who had developed diabetes during clozapine monotherapy). Gupta et al. found weight decline in patients switched from olanzapine to quetiapine after having gained more than 20% of their weight during olanzapine treatment. Twelve patients completed the 10-week study and lost a mean of 2.25 kg.
Risperidone has also been compared to other second generation antipsychotics regarding alterations of glucose metabolism. Recent reports did not indicate a significant risk for patients treated with risperidone.[27,32-39] Two further papers describe uncomplicated risperidone use in a total of three psychotic patients diagnosed with comorbid diabetes.[40,41]

Amisulpride

Up to now there is only one single case report,[42] describing transient hyperproinsulinemia in a patient in whom amisulpride had been added to clozapine. This patient had received clozapine as monotherapy before without any metabolic complications. However, until now, no studies investigated alterations of glucose metabolism in patients treated with this agent.

Ziprasidone, Aripiprazole and Zotepine

As yet, except for a case report about rhabdomyolysis, pancreatitis and hyperglycemia in a patient treated with ziprasidone,[43] there are no published data concerning adverse effects of these antipsychotics on glucose metabolism.

Lipid Changes During Treatment With Second Generation Antipsychotics

There is only a rather limited number of studies covering this issue. Five of the available reports are based on non-fasting lipid levels, which renders their interpretation difficult.[44-48]

The majority of case reports and studies published on clozapine[16,20,49-54] report an increase in triglyceride but not cholesterol levels. For olanzapine, two studies indicate an increase in triglyceride levels only,[55,56] whereas another study[22] and several case reports[57-60] point towards an increase in both cholesterol and triglycerides. Risperidone[61] and ziprasidone[62] have been shown to have little or no effect on plasma lipid levels. One case report describes zotepine-induced hypertriglyceridemia and hypercholesterinemia.[63] We found no reports about lipid changes during treatment with quetiapine, despite the fact that this agent has structural similarities to clozapine and olanzapine.[64]

The available data suggest that an increase in serum lipids is associated with an increase in body weight; therefore, agents associated with the lowest increase in body weight would also be expected to have a lower risk of induced serum lipid changes, but this has to be further investigated.

Conclusions and Recommendations

Recently published evidence in this field has a strong focus on clozapine and olanzapine, which are still considered to be the major offenders with regard to inducing metabolic adverse effects. This has also been the topic of a recent expert report prepared by the American Diabetes Association and the American Psychiatric Association.[65] The newer atypical antipsychotics - aripiprazole and ziprasidone - and also quetiapine, amisulpride and zotepine have been studied less well so far. Further studies need to include well-characterized probands in terms of baseline risk factors. The duration of exposure should be carefully controlled; ideally, drug naive patients should be included in study samples. In addition, there is a dire need to investigate the pathophysiology of antipsychotic-induced metabolic disturbances.

Given the serious health risks of disturbances of glucose and lipid metabolism, patients treated with antipsychotics should be subjected to appropriate baseline screening, as well as ongoing monitoring. According to the expert report cited above,[65] the following parameters should be considered respectively monitored:

1. personal and family history of obesity, diabetes, dyslipidemia, hypertension and any heart disease (baseline);
2. BMI (body mass index) at baseline and monthly until week 12, every 3 months thereafter;
3. waist circumference at baseline and annually;
4. blood pressure at baseline, after 12 weeks and annually thereafter;
5. fasting plasma glucose at baseline, after 12 weeks and annually thereafter;
6. fasting lipid profile at baseline, after 12 weeks and every 5 years thereafter.

According to the information obtained baseline, the psychiatrist should choose the antipsychotic, taking into account the probability of the development of metabolic side-effects. Clearly, if any pathological values are identified, the psychiatrist should not hesitate to refer the patient to a specialist. All of this will help to further enhance the safety and tolerability of using antipsychotic agents in the management of psychotic disorders.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


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** This is an important paper suggesting clinical guidelines concerning alterations of glucose and lipid metabolism.

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