

Metabolic Disturbances Associated With Atypical Antipsychotics

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Abstract

The atypical antipsychotics are less potent D_2 receptor antagonists than conventional antipsychotics and they have the distinctive feature of being 5-HT_{2A} receptor antagonists, which improves their neurological safety. Thus, they have demonstrated a diminished incidence of extrapyramidal side effects, but they are associated with the development of metabolic disturbances.

The occurrence of excessive weight gain (5 to 10 kg) mainly concerns clozapine and olanzapine, and to a lesser extent risperidone; the synergistic effects of histamine H₁ and serotonin 5-HT_{2C} antagonism have been postulated as the reasons for antipsychotic-induced weight gain.

New-onset diabetes and glucose intolerance are associated with the use of clozapine and olanzapine. There are many possible etiologies for the induction of insulin resistance by an agent: weight gain, dopamine which stimulates insulin secretion through an β adrenergic receptor stimulation mechanism.

Hypertriglyceridemia can occur during both clozapine and olanzapine treatment, generally after weight gain and perhaps related to an increase in serum leptin levels.

Risperidone is a more potent dopamine D_2 antagonist than clozapine and olanzapine. It may appear to have a lower propensity for metabolic side effects, except for therapy-induced hyperprolactinemia.

Keywords: Atypical Antipsychotics; Weight Gain; Glucose and Lipid Changes

Introduction

The management of schizophrenia, a common, chronic and incapacitating disease, was revolutionized in the 1950s by the discovery of antipsychotic drugs [1]. The leading drug at that time was chlorpromazine, used from 1952 onwards, which was remarkable due to the advances it led to in terms of the treatment of psychotic disorders, the benefits it provided to patients, the hopes that it raised, etc. No longer was it simply a question of calming down agitated patients: now the "hard core" of the disease was being dealt with, acting on the delusion itself. However, this action was accompanied by undeniable side effects, particularly extrapyramidal symptoms, psychomotor indifference and neurovegetative signs. These changes were actually a reflection of the therapeutic action of antipsychotics, demonstrating impregnation of the mesodiencephalic centres [2]. It was only 25 years later that the link between the clinical effectiveness

of antipsychotics and their affinity for D_2 dopaminergic receptors was made [3]. In fact, all antipsychotics demonstrate dopaminergic antagonism (binding to the D_2 receptors of the nucleus accumbens and the limbic system is responsible for the anti-delusional activity, while binding to D_2 receptors in the striatum is responsible for the extrapyramidal effects).

The discovery of the specific properties of clozapine [4], which differs from contemporary drugs through its effectiveness in resistant forms of schizophrenia and on deficit symptoms, opens the way for the development of "atypical" antipsychotics or "antipsychotics": olanzapine, risperidone, quetiapine, ziprasidone. Although dopaminergic antagonism remains the cornerstone of their action, these drugs (here we are talking about clozapine, olanzapine and risperidone) also have a serotonergic impact. We choose these drugs because we have now many studies about their metabolic effects. Their atypical nature lies in their high 5-HT_{2A}/ D_2 affinity ratio (strong blocking of 5-HT_{2A} and low blocking of D_2) [5]. Consequently, the dopaminergic hypothesis of schizophrenia is no longer univocal; there are interactions between dopamine and serotonin. The scope of action of these drugs is wider, with a definite antipsychotic effect, but also effects on mood, negative symptoms and cognition. In addition to these advances, they also induce fewer extrapyramidal side effects.

However, these three drugs are more often associated with metabolic signs than conventional antipsychotics.

Weight Changes

Weight gain is not specific to atypical antipsychotics and has been recorded since the use of chlorpromazine. However, it would appear that this risk is higher with the more recent drugs, particularly clozapine and olanzapine. Depending on the studies, it is estimated to affect up to 50% of patients, with an even greater susceptibility amongst children and adolescents [6].

The increase is the highest during the first year of treatment, with a mean weight gain of 5.3 to 6.3 kg for clozapine, and 6.8 to 11.8 kg for olanzapine [7]. It is the main side effect reported by patients treated with olanzapine. Individuals who are thin before treatment is instigated are more susceptible; this effect is identical in men and women and is sensitive to dietary control.

In a study it was shown a mean weight gain of 7% relative to baseline values in subjects treated for 10 weeks with clozapine

[8]. The extent of the weight gain with this drug may be partially due to the fact that, apart from its sedative properties, the patients taking it are generally those in whom the disease has been progressing for the longest time and who are the most sedentary. As with olanzapine, the weight gain is the most significant in subjects with a low starting weight. However, it is not easily controlled by dietary measures or physical exercise [9].

Risperidone is associated with lower weight gain, comparable to that observed with conventional antipsychotics. A retrospective study was conducted at the Oregon State Hospital in Salem, comparing olanzapine and risperidone in terms of metabolic disturbances [10]. In the two groups of patients (n=47) receiving one or other of these drugs, a significant increase in weight and Body Mass Index (BMI) is observed relative to baseline values during the first year of treatment. There is no significant difference between the two samples, although the mean weight gain is higher in the group receiving olanzapine. Being overweight classically exposes the subject to an increase in serum glucose and lipid levels; the above study does not highlight any correlation between the onset of diabetes or dyslipidemia and weight gain. Similarly, the study by Henderson et al. [9] does not reveal any correlation between weight gain and the development of diabetes but demonstrates a link between weight gain and an elevation in total cholesterol and triglyceride levels.

The source of this weight gain is related to several factors, ranging from the simplest and most obvious to the most complex: reduced physical activity inherent to the disease itself and the sedation induced by psychotropic drugs, antagonism of H1 receptors with a direct effect on appetite, 5-HT_{2C} serotonergic blocking leading to hyperphagia, resistance to leptin reflected by an elevation in its serum levels. Leptin is a cytokine produced by the adipocytes to regulate insulin secretion and energy metabolism via receptors in the hypothalamus, adipocytes and skeletal muscles [11]. Risperidone's lower affinity for H1 receptors may explain why the weight gain with this drug is significantly less than that observed with olanzapine and clozapine.

In addition to the medical complications directly linked to weight gain (increased risk of hypertension, dyslipidemia, insulin resistance, type-II diabetes, cardiovascular diseases, respiratory problems, gallstones, etc. and, ultimately, mortality), it should be noted that weight gain is associated with a higher level of non-compliance with treatment [12, 13].

Glucose Changes

These are thought to be linked to weight gain, the use of certain atypical antipsychotics (olanzapine and clozapine in particular), and perhaps to the schizophrenia itself, which represents a risk factor independently of the side effects of its treatment [14,15].

The spectrum of complications related to glucose metabolism ranges from moderate glucose intolerance to diabetic acidosis and ketosis, via numerous cases of new-onset diabetes due to insulin resistance (non-insulin-dependent or type-II diabetes). The development of acidosis and ketosis (defined by hyperglycemia, metabolic acidosis and ketonuria) is nonetheless a rare

occurrence in type-II diabetes, except for in specific conditions (stress, infections, etc.).

The cohort follow-up conducted by Henderson et al. [9, 16] for 5 years in patients treated with clozapine finds 36.6% with induced diabetes mellitus, the onset of which is not correlated with BMI or weight gain but with an increase in serum triglyceride levels.

The epidemiological study conducted by Koller et al. [17] looked at the time to onset of diabetes after the instigation of clozapine treatment: in 27% of patients, it occurred during the first month of treatment and in 56% during the first three months. This study also specifies that the time to onset and severity of the hyperglycemia is not related to the clozapine dosage administered. In the majority of cases, withdrawal of the treatment leads to a reversal of the disturbance, whereas reintroduction of the drug leads to deterioration in glucose values for most patients.

The study conducted in Salem [10] finds a significant increase in serum glucose levels after a year of treatment with olanzapine in comparison with baseline values. However, it does not reveal any significant difference between initial serum glucose levels and those after a year of treatment with risperidone. The difference between the two groups is significant, with a higher increase in serum glucose levels in the group treated with olanzapine.

The results of Koro et al. [18] suggest the same thing: patients treated with olanzapine have a significantly increased risk of developing diabetes in comparison with those who are not treated with antipsychotics or who are treated with conventional antipsychotics. For risperidone, the increase in this same risk is not significant.

Several mechanisms are put forward to explain the onset of glucose intolerance induced by clozapine [19]: it may involve a reduction in insulin-sensitive glucose transporters, an inability to stimulate recruitment of these transporters from the microsome to the plasmic membrane, or, lastly, a reduction in the response of β cells of the pancreas as a function of serum glucose levels, subsequent to blocking of 5-HT_{1A} receptors by atypical antipsychotics [20, 21]. In addition, by binding to β adrenergic receptors, dopamine may also stimulate insulin secretion [22].

Lipid Changes

These essentially involve elevations in serum triglyceride levels, sometimes to far above their normal values (>600 mg/dL) [23]. The first cases of hypertriglyceridemia in patients treated with clozapine were reported in 1996 by Ghaeli and Dufresne [24] and risperidone [25], and those with olanzapine in 1999 by Sheitman et al. [26]. Since then; numerous other studies have reported a significant elevation in serum triglyceride levels associated with treatment with olanzapine or clozapine.

The results of Henderson et al. [9] demonstrate, among other things, a correlation between weight gain induced by clozapine and an increase in serum triglyceride levels, without there being any significant increase in total cholesterol levels. A family history of dyslipidemia also plays a role in the onset of this metabolic disturbance.

The comparison made by Meyer [10] between these two groups of patients treated with either olanzapine or risperidone finds a significant increase in serum triglyceride levels in both samples, with a significantly greater risk for the group treated with olanzapine. There is no significant difference between total cholesterol levels either at the start or after a year of treatment with risperidone, but a significant elevation in cholesterol levels is observed for the group treated with olanzapine in comparison with the group treated with risperidone.

Some authors have revealed a correlation with weight gain, while others have concluded that there is a potential direct effect of these antipsychotics on serum lipid levels [7]. The mechanisms for this are not clear and the involvement of 5-HT₂ receptors or of leptin regulation remains uncertain [23].

Prolactin Changes

Hyperprolactinemia, a common endocrine disorder but largely underestimated, may be due to various causes, including treatment by many drugs. Antipsychotics play an important role in their occurrence. Their hyperprolactinemic potential is nevertheless variable, involving complex mechanisms. The increase in serum prolactin levels is a well known side effect of conventional antipsychotics [27].

This results from blocking of D₂ dopaminergic receptors in the tuberoinfundibular tract (28). The low affinity of clozapine and olanzapine for this type of receptors explains the limited elevation in serum prolactin levels induced by these two drugs. In contrast, risperidone strongly binds to D₂ receptors and, in this, is more similar to the conventional antipsychotics, inducing hyperprolactinemia, associated with their string of symptoms, both male and female (amenorrhea, irregular periods, anovulation, galactorrhea, sexual dysfunction, infertility, obesity, hirsutism, gynecomastia).

Hyperprolactinemia can even appear with low doses of risperidone (3.5+/-1.2 mg/d), and is reversible when treatment is discontinued [29].

Risk/Benefit Ratio

The benefits to patients of atypical antipsychotics in comparison with conventional ones are undeniable, both in terms of effectiveness on psychotic symptoms and associated moods, and in terms of improvement of quality of life and compliance with treatment.

The side effects of these new drugs are not negligible however, and should be foreseen or at least properly evaluated and treated when they occur.

There is no standard management for these metabolic disturbances induced by treatment: so what should be done if one of these complications subsequently develops when the patient appears to be fully benefiting from his/her treatment?

It is possible to intervene by means of lifestyle and dietary measures, which are often difficult or even unrealistic given the type of population concerned. Replacing one drug with

another is also a possible solution, but it is difficult to make this decision when the patient is suffering from treatment-resistant schizophrenia and is improved by clozapine.

The problem of excess weight can be handled by means of behavioural measures or specific drugs (amantadine, sibutramine, orlistat) when the patient is obese [1].

The resulting diabetes, not resolved by a suitable diet, can be treated like any type-II diabetes by biguanides, hypoglycemic sulfamides, and insulin if necessary, at the same time controlling the other cardiovascular risk factors.

As for hypertriglyceridemia, the first defence against this involves lifestyle and dietary measures, although these are sometimes insufficient, often making it necessary to prescribe fibrates.

Clinical and laboratory monitoring is essential in all cases.

Conclusion

The arrival of atypical antipsychotics has certainly not represented a revolution as important as the discovery properties of chlorpromazine in 1952 but nevertheless, it also significantly modified the

“Hospital landscape”, for example by decreasing considerably the number of patients stigmatized by their Parkinsonian pace. Through their words, patients also translate that evolution. The importance of therapeutic benefit for a patient given is based first of all on the evaluation of the benefit / risk, and the respective advantages or disadvantages of typical or atypical antipsychotics should be weighed in this perspective. Their appearance seems to be more of an evolution as a revolution, an “incremental” progress; one of the major enrichments brought by these products is undoubtedly the emergence of a consideration increased somatic state of these patients.

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