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WHAT EVIDENCE IS THERE TO SHOW WHICH ANTIPSYCHOTICS ARE MORE DIABETOGENIC THAN OTHERS?

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SUMMARY

Background: *The use of antipsychotic therapy has been proven to have an association with the incidence of diabetes mellitus. The use of atypical antipsychotics is shown to have a higher association, in contrast with typical antipsychotics. Olanzapine and Clozapine appear to have the highest rates of diabetes mellitus incidence, due to their tendency to affect glucose metabolism compared with other antipsychotic drugs. In this research the main goal is to understand which antipsychotic drugs are the most diabetogenic and to show the mechanisms involved in the glucose metabolism dysregulations with special focus on Olanzapine considering it is a very commonly prescribed and used drug especially among patients with schizophrenia.*

Methods: *Our study is a literature based research. For our research we reviewed 41 Pubmed published articles from 2005 to 2015.*

Conclusion: *According to most of the literature, from all the antipsychotics, Clozapine followed by Olanzapine appear to be the atypical neuroleptics that most relate to metabolic syndrome and Diabetes. The basis for this metabolic dysregulations appears to be multifactorial in origin and a result of the drugs, environment and genes interaction.*

Key words: *atypical antipsychotic – Olanzapine – diabetogenic – dyslipidemia – neurotransmitter – receptor – schizophrenia - metabolic dysregulations*

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by high blood sugar levels over a prolonged period of time. From all the types of DM, Type 2 DM is linked with unhealthy lifestyle behaviors, including diet, reduced physical exercise, tobacco use, increased body weight but can also be associated with other conditions, namely psychiatry diseases. It is estimated that Type 2 DM affects approximately 10% of people with schizophrenia. There is a relative risk estimating that people with schizophrenia are 2.5 times at increased risk of diabetes compared with the general population (Stubbs 2015). It is very important for diabetes to be diagnosed as early as possible, because it is a progressive disease and tend to worsen if left untreated. Therefore, there is a need for the multidisciplinary team to pro-actively screen and intervene to prevent and manage diabetes in people with schizophrenia. Patients with schizophrenia are treated on a daily basis with atypical antipsychotics and it is known that the potential of second generation antipsychotics to induce or trigger metabolic dysregulation, including type II diabetes mellitus and Metabolic syndrome, is firmly established (De Hert 2012).

Clozapine and Olanzapine - the most diabetogenic Antipsychotic drugs

After a systematic review of the literature it can be concluded that Atypical Antipsychoti induced diabetes does not always take a type 2 presentation in which weight gain and insulin resistance are implicated but also may present with diabetic ketoacidosis. When trying to understand the diabetogenic potential of each antipsychotic it is helpful to look at the retrospective database study conducted by Sernyak in 2002, that concluded that patients who received atypicals were 9% more likely to have diabetes than those who received typical neuroleptics.the prevalence of diabetes was proved to be significantly increased for patients who received Clozapine, Olanzapine, and Quetiapine, but not Risperidone (Volpato 2013). Also, numerous reports pointed out that glucose intolerance, ketoacidosis and T2DM frequently occur in patients receiving clozapine (Koval 1994), olanzapine (Ashim 2004; Gatta 1999), risperidone (Mohan 1999), quetiapine (Sobel 1999) and ziprasidone (Yang 2002). Among atypical antipsychotics there are marked differences exist in their diabetogenic potential. Olanzapine and Clozapine appear to have the highest tendency to disturb glucose metabolism compared with the other antipsychotic drugs available on the market (Volpato 2013) and when comparing the ranking reflecting the relative risk for weight gain, insulin resistance, dyslipidaemia and hyperglycaemia, clozapine and olanzanine have the highest risk, risperidone, quetiapine, amisulpiride and zotepine have a moderate risk; ziprasidone and aripiprazole have a lower risk (Newcomer 2005). Further studies which support this concept are those which show that Clozapine and olanzapine are more capable of inducing insulin resistance in peripheral tissues of animals (Albaugh 2006, Cooper 2005) and humans (Houseknecht 2007, Tulipano 2007) when compared with risperidone and quetiapine (De Hert 2012). Importantly, clozapine and

olanzapine appear to induce hyperglycemia (Koller 2002; McIntyre 2001), hyperinsulinemia (Vidarsdottir 2010) and insulin resistance (Henderson 2002; Lindenmayer 2001; Sowell 2003) shortly after the beginning of treatment (resolved on discontinuation of drug and reappeared with reinstitution of drug) (Koller 2002; McIntyre 2001). If we consider the importance of changes in the lipid profile and its consequences in metabolic dysregulation, Olanzapine has been proven to have the greastest propensity to increase cholestrol and lipids (Rummel-Kluge 2010) compared to the other atypical antipsychotics. Haloperidol has also similar effects on metabolic parameters but less than Olanzapine and Clozapine. Aripriazole and Amisulphride are relatively safer drugs when compared to other atipycal antipsychotics (Gupta 2014). In the CATIE study 2005, Olanzapine had the lowest rate of discontinuation but also showed the largest discontinuation due to weight gain or metabolic effects (Although in this CATIE study many of the patients were being prescribed above the licensed dose (Lieberman 2005)) (Table 1).

The multifactorial origin of diabetes and metabolic syndrome in patients taking atypical antipsychotics, namely Olanzapine

During our research we came across different findings about what could be the primary cause of the metabolic dysregulations seen in patients taking antipsychotic medication, and in special for olanzapine. Evidence was found that when talking about metabolic changes caused by atypical antipsychotic, patients with known risk factors for T2DM, such as ethnicity, first-degree family history of diabetes mellitus and baseline obesity, appear to be at increased risk for the development of glucose dysregulation during treatment (Jin 2004). Surprisingly, it was shown that 15% of patients have elevation of glycaemia with the first episode of schizophrenia, before starting the treatment and these alterations may be associated with increased intrabdominal fat and high levels of insulin and cortisol (Paula Rojas 2009). These findings suggest that schizophrenia is associated with metabolic alterations before the use of the antipsychotic medication, which leads to a greater risk of developing DM (Paula Rojas 2009). Also Jakovljević (2006) and Babić (2007) based on a Literature research found that metabolic syndrome occurs in 8-56% of patients suffering from bipolar disorder and that the incidence of Metabolic syndrome in other psychiatric diseases is: schizophrenia:19-63%, schizoaffective disorder 42%, depressive disorder 32-36%, chronic PTSD 31.9-35%. It is also important to notice that literature suggests that the young patients being treated with atypical antipsychotics have a significant increase in the prevalence of diabetes. The evidence supporting this idea comes from one systematic study that shows that in patients younger than 40 years old, all of the atypical antipsychotics were associated with a significantly increased prevalence of diabetes (Volpato 2013) and another study that shows that the risk of T2DM associated with antipsychotic drug consumption seems to be greatest in younger patients (usually ≤24 years) (Hammerman 2008). This findings can be explained by the fact that antipsychotic drugs have a greater orexigenic (appetite-enhancing) effect in children and adolescents than in adults (Kahn 2008).

The molecular mechanisms of action of antipsychotics - special focus on Olanzapine

The use of antipsychotic drugs may impair glucose metabolism by causing hyperglycemia, hyperinsulinemia and insulin resistance in adipose tissue, thereby increasing the risk of T2DM development. The two antipsychotics, olanzapine and clozapine, with the greatest effect on weight gain have also the highest association with impairment of glucose levels and studies suggest a common pharmacological mechanism (Miron 2014).

Effects on pancreatic cells

In most studies, hyperglycemia is considered to be secondary to weight gain and insulin resistance, however there have been reports of early and severe hyperglycemia and diabetic ketoacidosis, not explained by increase in weight, especially with the use of olanzapine and clozapine, which suggested that there is a direct effect of these drugs on the function of the pancreatic beta cell (Paula Rojas 2009).

Table 1. The risk of the different atypical antipsychotics to cause metabolic alterations regarding weight gain, DM and dyslipidaemia

Drug name	Weight gain	DM	Dyslipidaemia
Olanzapine	High	High	High
Clozapine	High	High	High
Risperidone	Moderate	Low	Low to moderate
Quetiapine	Moderate	Low to moderate	Moderate
Amisulpride	Low to moderate	Low to moderate	Low
Zotepine	Low to moderate	Low to moderate	Low to moderate
Aripiprazol	Low	Low	Low
Ziprasidone	Low	Low	Low

Clozapine and olanzapine are the drugs with the most marked metabolic effect, followed by risperidone, quetiapine, amisulpride and zotepine with intermediate effect, while the minor metabolic effects are seen with aripiprazole and ziprasidone

Besides patients treated with clozapine and olanzapine presenting with hyperglycemia and hyperinsulinemia, they also show elevated serum concentrations of glucagon, whose production by pancreatic α-cells is normally suppressed during hyperglycemia (Vidarsdottir 2010). These results suggest that atypical antipsychotics may simultaneously impair pancreatic α and β cells function (Vidarsdottir 2010).

Effects on neurotransmitters

The levels of mediator molecules as hormones that regulate the appetite and the function of the adipose tissue have been also studied: regarding Adiponectin (which is a protein produced in the adipocytes and that regulates insulin sensitivity) studies (Togo 2006), found no significant difference on its levels in patients with prolonged use of olanzapine and risperidone. Leptin was decreased in patients exposed to olanzapine for periods for less than four weeks (Togo 2006) and Ghrelin which is known to stimulate gastric acid production, which increases appetite had also decreased levels in patients exposed to olanzapine periods less than four weeks (Paula Rojas G 2009).

Changes of neurotransmitters and GLUT-transporters

Studies on Several neurotransmitters that are involved in food intake and body weight show that regarding 5-HT receptors, It is known that 5 HT1A agonists increase food intake and 5HT2C agonists decrease food intake. Olazanpine is known to be a strong 5HT2C antagonist, which can therefore lead to increase in food intake and weight gain/ (Miron 2014). For the D2 receptor Miron IC 2014 also found that, The D2 antagonism in hypothalamos, a joint effect of antipsychotics (including Olanzapine), can influence eating behaviour, with an increased food intake. Antipsychotics are also known to have a relative affinity for H1 receptors and Olanzapine due to the fact it has high affinity for the H1 receptors is associated with a high rate of weight gain (Miron IC 2014).The antagonism of α1 adrenergic receptor may contribute to weight gain by physical inactivity (Miron 2014).

For aripiprazole, quetiapine and ziprasidone this causal relationship with the receptors does not exist, for risperidone the results are intermediate and for clozapine and olanzapine a very high causal relationship is noticed (Miron 2014).

Also interesting enough and not only applicable to olanzapine is the fact that Regarding the interaction with other receptors it was found that The effect of antipsychotics is not limited to GLUT1, GLUT2 and GLUT3, but extends also to the insulin-sensitive GLUT4 (Ardizzone 2001). A decrease in GLUT4 mRNA expression and recruitment to cell surface may also be responsible for the inhibition of glucose transport in adipose tissue induced by antipsychotics treatment (Jassim 2012).

Neuronal changes supporting the negative effects of olanzapine in the metabolism

The effects of weight gain caused by antipsychotics may be at least partially mediated by the hypothalamus and it is known that the broadcast signal of the anorexigenic mechanism to the hypothalamus is disrupted by the antipsychotic medication (Miron 2014). Although antipsychotics have no effect on hypothalamic regions involved in the control of food intake, it was found that olanzapine increases expression of neuropeptide Y (NPY) in the arcuate nucleus (ARC) and that causes the BDNF signalling disruption that may cause increase food intake and obesity (Miron 2014). While still exploratory, studies (Stip 2012) also suggest that olanzapine treatment in humans induces changes in neuronal activity in specific brain regions, which correlate with levels of glucose, insulin, prolactin or the cholesterol/LDL ratio.

Genetic susceptibility

Several genes may be involved in the susceptibility to antipsychotics induced side effects, and the most consistent ones are those directly involved in the regulation of appetite and food intake, namely, melanocortin 4 receptor (MC4R), cannabinoid receptor 1 (CNR1), 5-HT2C receptor, NPY and leptin genes (Shams 2014, Gonçalves 2015).

The Importance of the changes in adipose tissue

Adipose tissue plays an important role in glucose and lipid metabolic pathways. Therefore, it has been proposed that the molecular mechanisms underlying the adverse metabolic effects of antipsychotic therapy may involve a dysregulation of adipose tissue (particularly the visceral one) homeostasis, namely, an increase in adipose tissue lipogenesis, differentiation/hyperplasia, secretion of pro-inflammatory mediators and insulin resistance and a decrease in adipose tissue lipolysis has been described in patients receiving antipsychotic medication and so they can be at risk of developing obesity, T2DM and/or cardiovascular disease (Gonçalves 2015). This conclusion comes from the fact that clozapine and olanzapine have been demonstrated to enhance lipogenesis in murine pre-adipocytes (Yang 2007, 2009) and adipocytes (Vestri 2007, Yang 2007), particularly in those located in white visceral adipose tissue and also to stimulate the initial stages of adipogenic differentiation in human adipocyte progenitor cells and increase triacylglyceride accumulation in differentiated cells (Hemmrich 2006, Pavan 2010). Also in particular clozapine, olanzapine, quetapine and resperidone, are also capable of increasing body weight and adiposity by decreasing adipose tissue lipolysis (i.e. triglyceride hydrolysis) (Ferno 2009, Minet-Ringuet 2007, Vestri 2007). Besides increasing lipogenesis and decreasing lipolysis, atypical antipsychotics are also able to stimulate the differentiation of preadipocytes into adipocytes,

Table 2. Mechanism of metabolic complications: Olanzapine

Weight gain	DM	Dyslipidaemia
▪ H1 receptor blockage ▪ 5-HT2C receptor blockage ▪ α1 adrenergic receptor blockage ▪ BDNF signalling disruption ▪ Genetic susceptibility ▪ (MC4R; 5-HT2C receptor; CNR1; NPY and leptin genes)	▪ Sedentary behaviour ▪ Increase appetite ▪ Weight gain ▪ Impairment of pancreatic cells ▪ Decrease in GLUT4 mRNA expression	▪ Hypothalamic dysregulation ▪ Anticholinergic activity ▪ Hyperprolactinaemia ▪ Weight gain ▪ 5-HT2A/ 5-HT2C antagonism

thus increasing adipose tissue mass (Hemmrich 2006, 2011). The balance between proliferation and differentiation of adipocyte progenitor cells is regulated by intracellular oxidative stress (Carriere 2004, 2003), and atypical antipsychotics increase mitochondrial ROS production (Bulua 2011) and oxidative stress levels in cells lines and tissues (Pillai 2007; Polydoro 2004; Schaffer 1998). In both rats and humans, clozapine and olanzapine appear to induce the greater degree of dyslipidaemia, followed by risperidone and quetiapine, whereas aripiprazole and ziprasidone do not seem to be associated with dyslipidaemia (American Diabetes Association 2004; Jassim 2012). Interestingly enough, adipocytes from olanzapine-treated rats tended to be larger (hypertrophic) (Minet-Ringuet 2007) and therefore more prone to rupture. This could result in the release of adipocytes content, e.g. triacylglycerides, into the circulation thereby increasing the risk of dyslipidaemia (Monteiro 2006).

Behaviour and metabolic dysregulations

There is a robust evidence demonstrating that higher levels of sedentary behaviour are associated with over a two-fold increased risk of T2DM mellitus and cardiovascular disease and people with schizophrenia are known to demonstrate high levels of sedentary behaviour (B. Stubbs 2015).

In schizophrenic patients, as the psychological condition improves, the appetite increases in general, which may lead to an increase in body weight, therefore it has been believed that the increase in body weight can be simply explained by the improvement of the psychological condition (Matsui-Sakata 2005) (Table 2).

DISCUSSION

There is a need to further explore the importance of genes that predispose individuals to metabolic dysregulations which can be aggravated with the start of therapy of antipsychotics. Likewise, there is also an increased need to analyse the impact of the psychiatric diagnosis in the predisposition to diabetes, since the data in literature is not clear enough. Lifestyle changes appears to be crucial to avoid this metabolic dysregulation, and there is a need to develop measures which help patients on antipsychotic therapy to reduce the risk factors for the appearance of metabolic changes and consequently T2DM. Clozapine shows the higher risk for the development of diabetes/metabolic syndrome according to most of the literature, however and interestingly more recent studies (Gupta 2014) present Olanzapine as the drug which has maximum potential to cause metabolic syndrome followed by Clozapine, Risperidone and Quetiapine, and therefore this clearly requires a more detailed review to understand what is behind the conclusions of this study and what was made in a different way compared to previous studies. Aripiprazole appears to be an excellent substitute for olanzapine, essentially to safeguard the younger population, considering their higher prevalence of diabetes incidence.

CONCLUSION

Diabetes mellitus is a group of metabolic diseases with multifactorial origin. It can be associated with uncounted illnesses, including psychiatrc diseases. People with schizophrenia are more susceptible to suffer from T2DM by itself than general population. However, the treatment with antipsychotic drugs, especially the use of the atypical neuroleptic drugs can lead to an increased risk of developing this condition. The antipsychotics induced weight gain can be concluded to be multifactorial in origin and develop from drug-gene-environment interactions, which result in a net change of balance between peptides and hormones regulating food intake and energy homeostasis (De Kloet 2010). When considering the metabolic effects of antipsychotics one must also consider as well the antipsychotic side effects such as sedation and muscle stiffness, decreased physical activity and energy expenditure, that may well be involved in the observed weight gain (Coccurello 2010).

Among atypical antipsychotics currently in use, clozapine and olanzapine are known to have the highest risk of metabolic complications.

According to literature when comparing Metabolic syndrome rates for Clozapine and olanzapine in relation with other antipsychotic agents, the highest rates of Metabolic syndrome were seen in those prescribed clozapine (51.9%) and the lowest rates in those who were unmedicated (20.2%) (Mitchell 2011, 2012). The drugs that present more insulin resistance index are: Clozapine (70%), Olanzapine (62%), resperidone (31%) and sulpiride (35%) (Wu 2008). Olanzapine appears to

have the greatest propensity to increase cholesterol and lipids (Rummel-Kluge 2010). Studies suggest that schizophrenia patients may be more vulnerable to olanzapine-induced weight gain and therefore, this findings may be explained not only by the drug treatment but one must also consider the addition of genetic predisposition for metabolic syndrome in these patients and that they have an especially high incidence of lifestyle risk factors for cardiovascular diseases, such as poor diet, lack of exercise, stress and smoking (Moteshafi 2012).

Even though the use of atypical antipsychotics predispose patients to metabolic dysbalances, it is crucial to focus on other risk factors, such as the unhealthy lifestyle choices, which are clearly underestimated. The adoption of a healthy-lifestyle, appears to be a major factor in preventing these metabolic disarrangements. It is imperative that the use of this medication come together with the encouragement of the patients to make some lifestyle changes if necessary, to reduce the side effects and the development of further co-morbidities.

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