

# A REVIEW OF THE EVIDENCE FOR THE USE OF METFORMIN IN THE TREATMENT OF METABOLIC SYNDROME CAUSED BY ANTIPSYCHOTICS

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## SUMMARY

**Background:** Psychiatric patients requiring therapy with antipsychotics have a greater incidence of becoming overweight or obese compared with the general population. Many of these patients are often treated with second-generation (atypical) antipsychotics (SGAs), which are associated with weight gain, dyslipidaemia, and other metabolic derangements. The most important and first line of treatment for the metabolic syndrome is lifestyle changes including diet and exercise. However, other approaches like the use of medication (e.g. Metformin) have been also used, mainly when the lifestyle changes are difficult to achieve. Therefore, the treatment of antipsychotic-induced weight gain with metformin may be an option after the lifestyle and dietary changes fail. The use of metformin is still experimental and off license regarding the treatment of metabolic syndrome in Psychiatric patients, however we wished to assess the evidence for its use.

**Methods:** Our study is a literature based research. For our research we reviewed 12 Pubmed published articles from 2006 to 2013.

**Conclusion:** Metformin have been reported to counteract effectively antipsychotic-induced body weight gain and has been demonstrated to improve glycaemic control and promote a moderate weight loss in both diabetic and non-diabetic subjects. Metformin use appears to be a benefit when started early in the course of treatment and mostly in young adults newly exposed to antipsychotic drugs.

**Key words:** metabolic syndrome - diabetes-lifestyle changes - metformin

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## INTRODUCTION

Individuals treated with atypical antipsychotics are more at risk of higher incidence of weight gain, dyslipidaemia, and metabolic syndrome which is a cluster of conditions - hypertension, hyperglycemia, increased waist circumference and abnormal cholesterol levels - that can occur together and lead to an increasing risk of cardiovascular disease, cerebrovascular accidents and diabetes mellitus.

The most important and first line for the treatment of the metabolic syndrome weights on the lifestyle changes including the diet and exercise. However, other approaches like the use of medication (e.g. Metformin) are also used, mainly when the lifestyle changes are difficult to achieve. Therefore, the treatment of antipsychotic-induced weight gain with metformin may be a good option after the lifestyle and dietary changes fail. Metformin is a biguanide, and an oral antidiabetic drug, used mainly for the treatment of type-2 diabetes mellitus, but can also be used for treatment of the metabolic syndrome, glucose intolerance and pre-diabetic conditions. Researchers show that metformin benefits can be similar to those of calorie intake restriction: this includes improved physical performance, increased insulin sensitivity, and reduced low-density lipoprotein and cholesterol levels (Block 2013). This occurs due to the fact that metformin increases AMP-activated protein kinase activity (an enzyme involved in cellular and

whole organism energy balance, glucose and fat metabolism AMPK), and also increases antioxidant protection, resulting in reductions in both oxidative damage accumulation and chronic inflammation (Block 2013). Apart from that, evidence also suggests that metformin may also act via mechanisms independent from AMPK. Metformin may partially enhance intracellular electron transport chain activity resulting in mitochondrial performance improvement (Block 2013). By altering energy production, metformin may lead to energy depletion, thus inducing glycolysis to maintain cellular metabolism and suppresses gluconeogenesis in the liver (Block 2013). Metformin is unlike other anti-diabetic drugs such as sulfonylureas because, instead of trying to squeeze more insulin out of your pancreas, “it acts by increasing the sensitivity of the hypothalamus and peripheral tissues (like muscles) to the effects of insulin. In effect, it rejuvenates this response, restoring the effects of glucose and insulin to much younger physiological levels” (Block 2013). Because a potential side effect of metformin is that it may cause malabsorption of vitamin B12 Metformin should be used with caution and under the supervision of their physicians by patients with compromised liver or kidney function, or congestive heart failure (Block 2013)

## METHOD

For our research we reviewed 12 Pubmed published articles from 2006 to 2013.

## RESULTS

Body weight gain and metabolic alterations are clinically relevant side effects of atypical antipsychotics. Olanzapine is an atypical antipsychotic agent associated with significant weight gain of above 7% of the baseline of body weight (Lieberman 2005) that is significantly higher than with other atypical antipsychotics except for clozapine (Komossa 2010). Considering that olanzapine is one of the most frequently prescribed drugs, with our research we tried to understand to what point metformin can be useful to decrease the incidence of weight gain and therefore prevent metabolic syndrome. Metformin has been reported to counteract effectively antipsychotic-induced body weight gain (Faulkner 2006, Baptista 2008, Maayan 2010). Metformin is particularly attractive because it is able to decrease body weight gain and improve insulin sensitivity, both of which are affected by olanzapine (Alamiri 2008).

During the research only one article contradicting this effects of metformin on body weight was found, but this article supports the evidence of positive effects of metformin in HOMA-IR in comparison to placebo (Baptista 2006).

Metformin has been demonstrated to improve glycaemic control and promotes a moderate weight loss in both diabetic and nondiabetic subjects (Seufert 2004, Wiernsperger 1999). In another systematic review and meta-analysis (Björkhem-Bergman 2011), metformin treatment caused a significant body weight reduction in adult non-diabetic patients treated with atypical antipsychotics and in children compared to placebo (Ehret 2010). The positive effects of metformin in young people are supported by a randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents (Klein 2006), which concluded that Metformin therapy is safe and effective in abrogating weight gain, decrease insulin sensitivity, and abnormal glucose metabolism resulting from treatment of children and adolescents with atypical antipsychotic (Ehret 2010.). In their meta-analysis on six studies reported that metformin significantly reduced weight, BMI, waist circumference and HOMA-IR as compared with placebo in those receiving atypical antipsychotics. An article supporting this results was published in 2010, which states that compared to placebo, the metformin group had significantly reduced weight (by 3.16 kg), BMI (by 1.21 kg/m<sup>2</sup>), waist circumference (by 1.99 cm), and HOMA-IR (by 1.71), (Ehret 2010). However the reduction in risk of diabetes was not statistically significant (0.30). In their meta-analysis comparing 15 agents for antipsychotic-induced weight gain, it was reported that metformin produced the greatest weight-loss, which remained significant when metformin was initiated after occurrence of weight gain, but not concomitantly with antipsychotics. In conclusion this analysis suggests that using metformin in patients treated with AAPs may reduce metabolic risks (Maayan 2010).

Another study concluded that young adults with schizophrenia newly exposed to antipsychotic drugs, who show a pattern of rapid weight gain and/or glucose dysregulation, are prime candidates for metformin if switching the antipsychotic medication to one with a lower metabolic burden is not an option or does not curtail the weight gain and/or adverse metabolic effects and metformin therapy should not preclude healthy lifestyle interventions (Hasnain 2011).

Miller (2009) reviewed the published evidence. He concluded that the rather limited data suggest that metformin may attenuate weight gain in both adult and adolescent patients taking atypical antipsychotics (Miller 2009). However, he pointed out that ‘most of the trials included foreign populations, were only 12-16 weeks in duration, and the dosage of metformin may not have been adequately titrated’ (Miller 2009). Therefore he concluded that ‘although the study results do not provide clear substantial evidence that metformin, as an adjuvant to atypical antipsychotic use, will decrease weight gain and improve metabolic effects, they are encouraging’ (Miller 2009). He therefore recommended further research (Miller 2009).

It is very important is to notice that when compared with other drugs approved for weight reduction such as orlistat and sibutramide, the weight reduction is higher with metformin (Rucker 2007).

## DISCUSSION

The use of metformin is still experimental and off license regarding the treatment of metabolic syndrome in psychiatric patients, but the studies performed with the intent to understand if metformin can be used to prevent metabolic syndrome seem encouraging. Also, metformin appears to be an option not only for when all the dietary and lifestyle interventions have failed, but as a concomitant therapy, with special beneficial effects when taken early in cases of patients that are treated with atypical antipsychotics and in young population.

## CONCLUSION

The use of atypical antipsychotics is associated with an increased risk of incidence of weight gain, dyslipidaemia, and metabolic syndrome. From all the atypical antipsychotics, olanzapine is the most associated with significant weight gain. The most important and first line of treatment for the metabolic syndrome is lifestyle changes, however new approaches such as the use of Metformin can also used, mainly when the previous changes are difficult to achieve. Metformin have been reported to counteract effectively antipsychotic-induced body weight gain and has been demonstrated to improve glycaemic control and promote a moderate weight loss in both diabetic and non-diabetic subjects. Metformin use appears to be of most benefit when started early in the course of treatment and mostly in young adults newly exposed to antipsychotic drugs.

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