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The Utility of Metformin in the Management of Metabolic Syndrome Induced by Atypical Antipsychotics

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Abstract

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1. Introduction

Metabolic syndrome is characterized by dyslipidemia, hypertension, central obesity, hyperglycemia, and insulin resistance. Together, these conditions lead to a significantly elevated risk of cardiovascular disease, type 2 diabetes, and cerebrovascular disease (1). All antipsychotic medications, particularly atypical or second-generation antipsychotics (SGAs), increase the risk for metabolic syndrome. The prevalence of metabolic syndrome in individuals taking antipsychotics ranges from 37% to 63% (2). The most significant metabolic side effects are associated with clozapine and olanzapine (3). In addition, diabetes and morbid obesity associated with SGA use may develop within as little as 6-12 weeks of treatment, whereas in the general population, these conditions typically take up to 5-10 years to manifest (3). Recent studies suggest that antipsychotics dysregulate glucose metabolism through CNS pathways, specifically through changes in the autonomic nervous system, neurotransmitter receptors, neuropeptide expression, AMP-activated protein kinase, and central insulin action (4). Moreover, antipsychotics block central glucose sensing, which impairs peripheral glucose metabolism (4).
Metformin is consistently utilized as a first-line medication in the treatment of type 2 diabetes. Its primary functions involve increasing insulin sensitivity, reducing gluconeogenesis, and increasing the peripheral uptake of glucose (5). Metformin is also being investigated as an adjunctive medication in patients using SGAs to attenuate insulin resistance and metabolic syndrome. Notably, metformin may lead to weight loss, reduced cardiovascular risk, and improved total cholesterol, LDL, and triglyceride levels. This review examines the efficacy of metformin in treating atypical antipsychotic-induced metabolic abnormalities, including insulin resistance and weight gain.

2. Discussion

Metformin's glucose-lowering properties, coupled with its ability to improve insulin sensitivity, may counteract the associated weight gain and glucose dysregulation that results from antipsychotic therapy. A recent study found that 78.8% of patients using first- and second-generation antipsychotics have an elevation in their baseline

doi: 10.46570/utjms-2025-1676 weight by > 7% (6). This raises a major concern regarding the metabolic changes associated with antipsychotic use. However, metformin may be a solution to this challenge. A meta-analysis was performed using global data from 14 studies that investigated the concomitant initiation of metformin with an antipsychotic, which found a statistically significant reduction in the weight gain with metformin (−3.12 kg) when compared with the placebo group, resulting in a 5.1% reduction in body weight change (7). A second meta-analysis of 12 studies found a mean difference in weight between metformin-treated and placebo groups of -3.27 kg (8). In addition, metformin was more efficacious in stopping weight gain when initiated prior to the development of insulin resistance compared to patients with chronic antipsychotic use who have already undergone weight gain (8). Taken together, these studies suggest that metformin may have greater efficacy in antipsychotic-naive patients to proactively stop weight gain. A different double-blind study was performed to evaluate the administration of metformin to attenuate olanzapine induced weight gain in drug-naive patients with schizophrenia. This study demonstrated that only 16.7% of subjects in the metformin group gained >7% of their initial body weight, compared with 63.16% in the control group, highlighting a substantial difference in weight gain between the two groups (6). According to current guidelines, weight loss of > 7% is the cutoff point for clinically significant weight gain (6). These findings suggest that metformin led to a statistically significant as well as clinically significant reduction in weight gain, which may attenuate the associated morbidity and mortality.

The current guidelines recommend obtaining baseline screening before or shortly after the initiation of any antipsychotic medication, including BMI, waist circumference, blood pressure, fasting glucose, and lipid profile. BMI should be reassessed at 4, 8, and 12 weeks after SGA initiation, and quarterly thereafter. Fasting glucose, lipid profile, and blood pressure should be reevaluated at 3 months, followed by annual assessments of blood pressure and plasma glucose, and lipid testing at 5-year intervals (9). Despite these guidelines, however, monitoring practices have been reported to be suboptimal (9).

The first evidence-based guidelines
were recently published recommending metformin

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for preventing antipsychotic-induced weight gain (AIWG). They recommend co-initiation with high-risk antipsychotics (olanzapine, clozapine), co-initiation with medium risk antipsychotics (quetiapine, paliperidone/risperidone) in patients aged 10-25 years or with cardiometabolic risk factors, and commencement with any antipsychotic if baseline weight increases >3% within the first year (10). Despite these novel guidelines, shared decision-making, a collaborative process between healthcare professionals and patients to make decisions about their care, will be necessary for implementation (10).

3. Conclusion

This review highlights metformin use as an advantageous adjunctive therapy in mitigating the metabolic dysfunction associated with second-generation antipsychotics, particularly weight gain and insulin resistance. Meta-analyses and clinical trials consistently demonstrate that metformin leads to statistically and clinically significant reductions in weight gain, notably when initiated early in treatment. Newly established guidelines for concomitant use of metformin in managing antipsychotic-induced metabolic effects represents an important step toward standardizing care, though successful implementation will rely on shared decision-making and continued evaluation.

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