

Metabolic Abnormalities Linked to Antipsychotic Medication Therapy in Schizophrenia Patients

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Abstract. For many years, people with schizophrenia have been shown to have serious metabolic problems, such as clinically substantial weight gain, hypertension, and disruption of glucose homeostasis. A significant treatment challenge for physicians is weight gain brought on by antipsychotics. In research studies, obesity and weight gain have been linked to a number of unfavorable outcomes, such as poor medication adherence, a higher risk of cardiovascular and cerebrovascular disorders, higher death rates, and a lower quality of life. Due to metabolic problems and obesity, patients with schizophrenia have a significantly lower life expectancy and higher death rates than people in the general population. While almost all antipsychotic medications are known to cause weight gain, the extent of this weight increase varies widely. Patients typically experience a rapid initial weight gain shortly after starting antipsychotics, and this trend continues over the long term. However, the exact mechanisms by which antipsychotics lead to metabolic issues and weight gain remain unclear. Despite the fact that there are protocols for identifying and tracking metabolic issues brought on by antipsychotics, these recommendations are not consistently applied in clinical practice. Various studies have also explored strategies to manage metabolic issues associated with antipsychotic use. However, due to the substantial clinical variation in both mental and metabolic symptoms throughout the course of the patient's illness, the findings in this area remain a subject of debate. In this narrative review, we offer a comprehensive examination of both classical and contemporary literature on metabolic concerns related to schizophrenia, focusing on the propensity of several antipsychotics to promote weight gain.

Keywords: Metabolic disorder, schizophrenia, antipsychotics, weight gain.

1. Introduction

People with schizophrenia have a death rate that is two to three times greater than the normal population., and their life expectancy is approximately 20-25% shorter than that of individuals without the condition. Besides a significantly elevated risk of suicide, cancer, and various other systemic diseases, metabolic syndrome and obesity stand out as significant cardiovascular risk factors for those diagnosed with schizophrenia. Research has indicated that heightened levels of fasting and post-meal glucose in drug-naïve individuals with schizophrenia are linked to the severity of their condition. While aspects of this metabolic dysfunction can be attributed to an unhealthy lifestyle, there is also evidence suggesting shared underlying physiological mechanisms between schizophrenia and metabolic disorders.

In individuals who have been diagnosed with schizophrenia or psychosis, weight gain can be attributed to a variety of factors. Key contributing factors are believed to include limited exercises, unhealthy diet, genetic factors, and the use of antipsychotic medications. Weight gain resulting from antipsychotic medication, often referred to as antipsychotic-induced weight gain (AIWG), presents a significant challenge in the treatment of individuals with mental health conditions. Antipsychotic medications can also lead to weight gain, disruptions in glucose metabolism, increased triglyceride and cholesterol levels, hypertension, and the onset of metabolic syndrome. Over the next five to ten years, this can lead to a doubling of the risk of diabetes and a tripling of the risk of cardiovascular disease. Before initiating antipsychotic treatment, examinations of individuals experiencing their first episode of schizophrenia and those who have not previously used medication have revealed issues with glucose regulation and subtle abnormalities in lipid levels. Impaired glucose tolerance is another

factor supporting the link between schizophrenia and metabolic problems in first-degree relatives of those with schizophrenia.

For individuals with schizophrenia, the use of antipsychotic medications can exacerbate metabolic irregularities. The recommended medication for treating schizophrenia patients is an antipsychotic, which is also used to treat other mental illnesses such bipolar disorder, depression that is resistant to therapy, Tourette's syndrome, and violent conduct in autistic people. First-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) are two categories for these drugs. FGAs exert their effects by inhibiting dopamine type 2 (D2) receptors in the dopaminergic system. SGAs, when administered at clinically effective doses, are less likely to induce extrapyramidal symptoms compared to FGAs and demonstrate greater efficacy in addressing the mental illness's detrimental emotional, cognitive, and behavioral manifestations. It's important to note that, despite a meta-analysis finding that almost all antipsychotics cause weight gain over time, some SGAs are more likely to have this side effect than highly effective FGAs.

While antipsychotic medications are essential for managing schizophrenia, it is crucial for doctors to carefully assess the pros and cons before determining the most suitable treatment approach. Often, clinicians do not fully consider the potential for weight gain and its consequences when prescribing antipsychotics. Patients prescribed antipsychotics often do not receive sufficient monitoring of their body weight and other factors related to metabolic risks. This article explores the side effects of antipsychotic drugs on weight gain and metabolic concerns.

2. Antipsychotic Drugs Associated Metabolic Disturbances

2.1. Antipsychotics and weight gain

The increasing prevalence of obesity in the general population has heightened the severity of the issue and raised awareness about it. Kraepelin had previously recognized the prevalence of weight increase and obesity in people with schizophrenia. Obesity in individuals with schizophrenia began to raise concerns around the 1950s with the introduction of antipsychotic medications like chlorpromazine, leading to a phenomenon of "widespread obesity" in psychiatric institutions. However, the weight gain caused by antipsychotic drugs made the movement disorders (dyskinesia) intolerable for patients. The advent of second-generation antipsychotics, starting with clozapine, resulted in such a minimal occurrence of extrapyramidal side effects (EPS) among patients that it became necessary to focus on the metabolic side effects of these drugs.

2.1.1 Body data change

Researchers have assessed the impact of medications on impaired glucose tolerance, dyslipidemia, and other features of the metabolic syndrome by comparing drug-naïve schizophrenic patients with healthy controls. In a case-control study conducted in 2016 involving drug-naïve individuals with schizophrenia, approximately a quarter of the patients displayed inferior baseline glucose tolerance when compared to the control group. Additionally, individuals with schizophrenia exhibited higher levels of insulin resistance (IR) and fasting blood sugar levels than controls. Notably, individuals with schizophrenia had higher values for body mass index (BMI), triglyceride (TG) levels, low-density lipoprotein (LDL) levels, waist circumference, and hip circumference in comparison to controls. It is important to emphasize that these anthropometric measurements were dissimilar between patients and controls even before any medication was administered. Similar findings were observed in adolescents through the most recent Antipsychotic Medication Tolerance and Efficacy (TEA) study. Drug-naïve individuals experiencing their first episode of psychosis, aged 12 to 17 years, exhibited greater waist circumference, total cholesterol, LDL, and non-HDL levels when compared to controls.

Another case-control research including drug-naïve people found that those going through their first psychotic episode had greater levels of insulin and C-peptide and lower levels of high-density lipoprotein (HDL) compared to controls who were the same age and BMI. This indicates that individuals with psychosis still exhibit increased insulin resistance (IR) compared to healthy controls,

even after accounting for any potential effects that schizophrenia itself might have on BMI. Importantly, there were no notable differences in triglyceride levels, total cholesterol, or fasting blood sugar levels between patients and controls when considering BMI.

The study also acknowledges the possibility that the use of antipsychotic medications may heighten the risk of metabolic issues. The findings also show a greater prevalence of obesity (defined as a body mass index (BMI) > 30 kg/m²) in people with schizophrenia. However, as previously established, individuals with schizophrenia had an elevated baseline risk of metabolic syndrome even before initiating antipsychotic medication.

According to a meta-analysis of 48 trials, individuals who were previously antipsychotic-naïve had a relatively low prevalence of metabolic syndrome at just 10.2%, in contrast to 19.4% in the aripiprazole group and 47.2% in the clozapine group. This provides additional evidence that the condition of the illness itself contributes to the adverse metabolic symptoms in addition to the effects of pharmacological therapy. Antipsychotic medications are known to have a well-documented side effect affecting 15–72% of individuals with schizophrenia, which is weight gain. First-generation antipsychotics like chlorpromazine and thionitrazine, while less effective than haloperidol and fluphenazine, are more likely to lead to weight gain.

2.1.2 Glucose intolerance

Antipsychotic medications elevate the risk of developing diabetes and glucose intolerance, and understanding the intricate mechanisms involved in glucose regulation is essential. Maintaining glucose homeostasis depends heavily on the coordination of several organs, including the liver, pancreas, adipose tissue, skeletal muscle, and the brain. Moreover, several peripheral and central systems, encompassing hormones, neurotransmitters, and nutritional factors, which interface with the autonomic nervous system, collaborate to execute this critical function.

The central nervous system disruptions induced by antipsychotic medications may lead to glucose intolerance. Second-generation antipsychotics, frequently employed in the treatment of mental disorders, are noteworthy in this regard. Compounds found in these medications, like olanzapine, possess the potential to induce adverse metabolic effects such as diminished glucose tolerance and insulin resistance. The use of antipsychotic drugs has been linked to type 2 diabetes and reduced glucose tolerance, particularly in individuals characterized by factors like age, specific neuropsychiatric conditions, and abdominal obesity.

Notable medications in this context include chlorpromazine, clozapine, and olanzapine. The extent of the association between antipsychotics and diabetes varies depending on the specific drug, with chlorpromazine, clozapine, and olanzapine exhibiting more pronounced effects. Some of the alterations in glucose metabolism associated with these treatments can be attributed to increased abdominal fat. However, case studies and recent controlled research suggest that clozapine and olanzapine may potentially exert detrimental effects on glucose metabolism independently of obesity. In fact, nearly all antipsychotic drugs have been linked to glucose intolerance, with haloperidol, clozapine, and olanzapine in the risperidone ratio demonstrating the most potent effects.

Furthermore, these medications can lead to elevated plasma catecholamine levels, with norepinephrine exerting the most significant impact. Clozapine has also been shown to increase epinephrine levels. When compared to risperidone, olanzapine appears to be more influential than haloperidol in this regard. In summary, antipsychotic medications, while essential for the management of mental illnesses, come with a range of metabolic side effects that impact glucose regulation and warrant careful consideration.

2.2. Antipsychotic drugs and metabolic disturbances related diseases

2.2.1 Effect of insulin

Antipsychotic medications (APs) have been associated to insulin resistance, which is defined by increased levels of insulin and related peptides in individuals with schizophrenia. The body's energy balance is mostly governed by insulin. It interacts with receptors in the arcuate nucleus of the

hypothalamus and is produced by beta cells in the pancreas. Glycogen, which is converted to glucose by glucagon and stored in the liver under the influence of insulin, helps maintain overall glucose balance.

Insulin resistance, which impacts the effectiveness of insulin in the muscles, liver, and adipose tissue, is closely linked to abdominal fat deposition more than other forms of adiposity. Among these tissues, muscle tissue utilizes the majority of consumed glucose, accounting for approximately 80% of its uptake. This condition raises the risk of both diabetes and cardiovascular disease. Furthermore, APDs can affect histamine and toxin receptors, leading to decreased insulin secretion due to cholinergic stimulation, disruption of the leptin signaling pathway, and the development of insulin resistance.

Antipsychotic drugs (APDs) act on various biological targets, including serotonin and histamine receptors. However, all therapeutically effective APDs primarily influence dopamine D2 and D3 receptors. This suggests that these receptors not only play a pivotal role in enhancing the therapeutic effects of these medications but may also be significant contributors to the metabolic side effects associated with these treatments. D2R receptors are expressed in lactotrophic cells of the pituitary gland, responsible for producing and secreting prolactin. Prolactin effectively regulates systemic glucose homeostasis, and D2R modulates the proliferation of lactotrophic cells. D2R is also connected to the striatal reward circuit, which regulates the central regulation of hunger. Increased hunger, increased food consumption, and the emergence of obesity have been related to D2R mutations or polymorphisms associated with reduced levels of D2R in the central nervous system.

D2R signaling and dopamine in the hypothalamic region may influence circadian rhythms involved in metabolic regulation, including systemic insulin sensitivity. These intricate interactions highlight the complex relationship between antipsychotic medications, neurotransmitter systems, and metabolic consequences in individuals with schizophrenia.

2.2.2 Affecting pancreatic beta cells

Beta-cells have drawn more attention in recent years as a side effect of APD-induced schizophrenia therapy. The only cells in the body that can release insulin are beta cells. APD may harm cells directly or indirectly. Numerous methods by which APD results in β -cell dysfunction have been shown in previous investigations (Figure). APD may affect a number of beta cell receptors, reducing the body's ability to secrete insulin. Only prazosin and md100907, according to the study, were linked to decreased insulin secretion. By attaching to these receptors, olanzapine may prevent them from promoting insulin secretion. It has been demonstrated that a key indication of APD-induced metabolic disorders like diabetes is the affinity of antagonists for the m3 receptor. It has been demonstrated that APDs with a high affinity for M3 receptors, such as olanzapine and clozapine, decrease insulin production, demonstrating the critical role M3 receptors play in the direct action of apd on beta-cells.

Additionally, it has been demonstrated that APD is linked to an increase in beta cell apoptosis, which lowers beta cell quality and lowers insulin output. As a result, there are fewer beta cells, which causes insulin secretion to decline. The destruction of beta cells by one of them, clozapine, has been demonstrated to cause diabetes. Further research is needed to understand how APD affects beta cells' mitochondria. This might provide insight into the primary cause of diabetes caused by APD.

2.2.3 Other metabolic syndromes

Antipsychotic medications are helpful for a variety of diseases, including schizophrenia, but it is important to be aware of their negative side effects. For a long time, several metabolic problems linked to antipsychotics have received a lot of discussion and attention. Antipsychotic users of all ages have metabolic syndrome, but atypical antipsychotic medication in children and adolescents makes them particularly vulnerable to these adverse effects. Type 2 diabetes and obesity-related metabolic illnesses may both contribute to teenagers' decreased academic and professional prospects. According to studies, teenagers with metabolic syndrome have lessened brain lobe structural integrity and worse cognitive function than healthy adolescents.

(1) Phenothiazines

Olanzapine and quetiapine, two atypical antipsychotics, have been linked in studies to higher triglyceride and total cholesterol levels. Notably, ziprasidone and risperidone were linked to lower triglyceride and cholesterol levels, while triglyceride levels in clozapine patients were nearly twice as high as those in patients receiving traditional antipsychotics. Blood lipid side effects from aripiprazole and ziprasidone were negligible, and they even reversed dyslipidemia brought on by prior antipsychotic therapy.

(2) Typical and atypical antipsychotics for metabolic syndrome

While second-generation antipsychotics (SGAs), whose impact on metabolic symptoms may have been underappreciated, have been the focus of the majority of research on metabolic syndrome, numerous investigations have failed to find any differences between individuals receiving SGAs and those taking traditional antipsychotics in the occurrence of metabolic syndrome. A study comparing the effects of olanzapine with haloperidol in patients with first-episode psychosis lends credence to this idea. After two years on olanzapine, individuals with first-episode psychosis—a group of patients with very little prior therapy and persistent symptoms—gained an average of 15.4 kg of body weight, compared to 7.5 kg for those taking haloperidol. Large weight gain may indicate that typical antipsychotics are linked to metabolic problems and weight gain.

(3) Diabetes Mellitus

The use of antipsychotic medications poses a significant metabolic challenge leading to the development of diabetes. It is believed that between 16% and 25% of people with schizophrenia have diabetes overall, making them two to four times more likely to have diabetes and obesity than the general population. The majority of new instances of type 2 diabetes within the first six months of therapy are caused by antipsychotics, and these cases are frequently accompanied by significant weight gain or obesity. Additionally, a family history of the condition is associated with a higher risk of diabetes in this group of people.

A population-based study including case-control revealed a broad spectrum of diabetes risks associated with antipsychotic use. The risks associated with olanzapine and risperidone were found to be 4.2 and 1.6 times higher, respectively, compared to certain other medications. Notably, the risks associated with no treatment were 5.8 and 2.2 times higher. In younger patients, quetiapine appears to have a higher likelihood of being linked to diabetes compared to traditional medications, with chlorpromazine and thionitrazine showing a weaker association than olanzapine or clozapine. These findings align with the results of several large retrospective population studies. When compared to the control group, obese women had higher fasting blood glucose levels than those who were not fat, and haloperidol has been proven to cause insulin resistance, impaired glucose tolerance appeared to be more prevalent in the aliphatic phenothiazine group than in the fluphenazine or haloperidol groups.

Various hypotheses have been proposed to explain antipsychotic drug-induced diabetes, although none have been definitively proven. Diabetes that develops without weight gain is closely linked to drug-induced weight gain. Hypotheses include the impact of antipsychotic drugs or interference with the hypothalamus' ability to regulate blood sugar levels due to hypothalamic dopamine antagonism. Other pathways contributing to effective anticholinergic-induced insulin secretion regulation involve increased triglyceride levels, weight gain, leptin resistance, heightened peripheral tissue insulin resistance due to hyperprolactinemia, and 5-HT_{2A}/5-HT_{2C} antagonism.

3. Conclusion

Together, the studies suggest a potential link between antipsychotic drugs and metabolic irregularities and weight gain, which are important risk factors for cardiovascular disease in schizophrenia patients. In general, SGAs are more likely than FGAs to develop metabolic problems. Aripiprazole, Ziprasidone, and Lurasidone fall into the lowest risk category, while SGAs with the highest risk of weight gain are clozapine and olanzapine.. Other SGAs include Quetiapine,

Risperdone, and Paliperidone, which fall into the middle risk category. Since these targets could be dependent on signaling molecules and pathways (like dopamine), their interruption or modification in one organ is likely to affect other organs as well, which explains how many systems are interrelated. Due to APD-induced preexisting schizophrenia, metabolic problems are more likely to develop. APD causes significant metabolic dysfunction when combined with other lifestyle and environmental variables.

Despite medical recommendations, metabolic and cardiovascular risk variables have not been sufficiently evaluated in antipsychotic-treated patients. Psychiatrists and other caregivers should also encourage patients to lead healthy lifestyles that include exercise and a balanced diet. Adjunct drugs to prevent weight gain or switching to another low-metabolic risk antipsychotic may be a useful alternative if lifestyle changes are not obvious. All therapies should be well monitored because some individuals' responses to these medicines and medications might be unpredictable. Therefore, enhancing our knowledge of the processes governing metabolic control and schizophrenia may reveal shared pathways between the two, eventually guiding the development of novel medication options.

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