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A Review on Glycemic Intolerance Associated with use of Antipsychotics

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ABSTRACT

Background:

The prevalence of diabetes and other cardiometabolic disorders in psychiatric patients is relatively high when compared to the general population. Various researches suggest the predominant role that antipsychotics play in the development of such abnormalities among other factors.

Purpose of review:

This review examines the existing latest clinical evidence suggesting the role of antipsychotics in the development of glycemic intolerance and looks for a comprehensive explanation. The risk of cardiometabolic disorders is one of the leading causes of morbidity and mortality and the psychiatric population is relatively at an increased risk than the general population. Antipsychotics affect glucose homeostasis by directly affecting various receptor activities which are discussed in this review.

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Summary:

The clinical implications of glycemic intolerance due to antipsychotic use are weight gain and other cardiometabolic abnormalities which significantly influence the mortality and morbidity of psychiatric patients. It is important to establish concrete screening measures and management guidelines for the early diagnosis and management of antipsychotic-induced glycemic intolerance and other cardiometabolic abnormalities. Further research is needed to establish the role of antipsychotics in glycemic intolerance to improve the management strategies of diabetes in patients with severe mental disorders.

Keywords:

Glycemic intolerance; Diabetes mellitus; Antipsychotics; Weight gain; Insulin resistance.

INTRODUCTION

In today's world, the incidence of mental illness is more common than most people think. The World Health Organization reported that around 25% of the living population are prone to be affected with some kind of mental illness at some point in their lives(1). The spectrum of illness varies from mild anxiety to more severe psychiatric disorders such as schizophrenia and Bipolar disorder. However, the evolution of modern medicine has opened a vast multitude of treatment choices for managing psychiatric disorders. One such class of therapeutic agents is called Antipsychotics, and as the name suggests these are agents primarily used to control or manage a wide range of psychosomatic symptoms presenting with the illness(2). As these psychiatric disorders tend to worsen without proper management measures, they must be treated appropriately. Psychiatrists around the world agree that antipsychotics are the most effective agents that can ameliorate various psychiatric symptoms such as aggression, hallucination, and others. Antipsychotics are also capable of creating a wide range of side effects that include Stiffness and shakiness, uncomfortable restlessness (akathisia), movements of the jaw, lips, and tongue (tardive dyskinesia), sexual problems due to hormonal changes, sleepiness and slowness, weight gain, a higher risk of getting diabetes, constipation, dry mouth and blurred vision(3–8). Due to various reasons that are still under discussion, antipsychotics work differently on different patients so the severity, frequency, and incidence of these side effects may not be similar in all patients(9). However, most psychiatric patients experience at least any one of the side effects.

One such common and predominant side effect associated with the use of antipsychotics is Diabetes mellitus or Glycemic intolerance which is the main focus of the review. Glycemic intolerance can be defined as a metabolic abnormality that increases blood sugar levels or

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dysglycemia that comprises both prediabetes and diabetes(10). This includes impaired fasting blood glucose and impaired glucose tolerance and diabetes mellitus. Glycemic intolerance must be taken seriously because metabolic disorders such as diabetes mellitus, hypertension, dyslipidemia, and other cardiovascular disorders are the leading cause of morbidity and mortality in the general population(11). Since the development of glycemic intolerance is an undesirable effect of using antipsychotics, the psychiatric population becomes the people at risk inevitably(12,13). Monitoring the metabolic functions of psychiatric patients is a wise technique to identify and manage any abnormalities beforehand. The incidence of glycemic intolerance and other metabolic disorders are supported by several clinical studies that prove its risks in antipsychotic users(12,14–18). However, the development of glycemic intolerance could have been an outcome of poor lifestyle, diet, and physical inactivity which need to be carefully assessed in the risk population. This review focuses on discussing the role of antipsychotics in the development of glycemic intolerance and its consequences.

History of antipsychotics

Antipsychotics are a class of medications primarily used for the management of psychosis, delusions, hallucinations, and paranoia(2,8). They are also known as neuroleptics and used together with mood stabilizers in the treatment of the bipolar disorder. Atypical antipsychotics, known as first-generation antipsychotics, were started using as medication by 1933 in France(19). The study on developing antihistamines progressed into the discovery of Promethazine in 1947, due to the sedative effects of the drug they were used in surgeries. Soon after derivatives of promethazine were studied and altered which led to the introduction of chlorpromazine in 1950(20). The second-generation antipsychotics also called atypical antipsychotics to include clozapine, olanzapine, risperidone, and related derivatives(21). The second-generation antipsychotics have less effect on motor movements than the first generation(22). Both the generation works by blocking the dopamine receptors in the brain, but second-generation antipsychotics tend to act on serotonin receptors as well. Clozapine the first atypical antipsychotic initiates activation of NMDA receptors and thereby activating glutamate and clozapine blocks only about 30-40% of dopamine receptors(23).

General mechanism of glycemic intolerance

The amount of glucose in the body is strictly regulated by insulin and glucagon. In an overnight fast of more than 10 hours, the glucose in the liver is produced mainly by glycogenolysis and gluconeogenesis, this is called endogenous glucose production (EGP)

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which is correlated to both fat-free mass and fasting plasma glucose (FPG) concentration(24). During a postprandial state, the amount of insulin is increased and glucagon level is decreased causing a suppression in EGP. During the primary stage of glucose intolerance, the beta cells produce insulin to maintain the glucose in the normal range, but as the condition advances the beta cells are not able to sustain the normal insulin secretion and thereby producing glucose intolerance(25). Both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are conditions that cause insulin resistance due to beta-cell dysfunction(26). The fasting plasma glucose level will be higher in glucose-intolerant individuals than in those with normal glucose tolerance as a result of insulin resistance. IFG and IGT, the two subdivisions of glucose intolerance have different sites and patterns for insulin resistance and insulin secretion(27). IFG is mainly characterized by hepatic insulin resistance and muscle insulin sensitivity whereas IGT is predominantly associated with muscle insulin resistance.

Role of antipsychotics in development of glycemic intolerance

Weight gain is one of the most common consequences of taking neuroleptics and atypical antipsychotics. Diabetes induced by these antipsychotics is also one of the consequences of weight gain. Atypical antipsychotics like clozapine and olanzapine have the highest chance of causing weight gain and diabetes(28). The diabetic status of the patient can be improved by removing the suspected antipsychotics from the treatment plan but there won't be much reduction in weight gain and can recur immediately once the drug is started. In a study done by *Cagliero et al* on non-obese patients with schizophrenia, an intravenous tolerance test was done to test the acute effects caused by clozapine, risperidone, and olanzapine(29). The study showed that clozapine has higher 20-minute glucose levels than risperidone and insulin sensitivity was higher in those taking risperidone than clozapine and olanzapine. This study shows that diabetogenicity is a result of pharmacological action rather than diabetes being a secondary or indirect effect caused by weight gain.

Studies show that certain antipsychotics inhibit the glucose transport into PC12 cells resulting in an increase of GLUT1 and GLUT3 glucose transporter isoforms(30–32). This in turn would increase the release of insulin as a consequence of hyperglycemia. Prolonged hyperinsulinemia eventually leads to insulin resistance and further glycemic intolerance progressing to prediabetes and diabetes mellitus as a result of downregulation of insulin receptors.

Another hypothesized mechanism through which antipsychotics induce glycemic intolerance is receptor antagonism. Both atypical and typical antipsychotics affect the effects of

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neuropeptides such as serotonin and dopamine through respective receptor antagonism(33). Receptors such as the 5-HT_{2c} receptors are probably involved in the regulation of various hormonal signals that regulate food intake and satiety(34). And relative antagonistic activity at 5-HT_{2c} receptors could explain the weight gain potential of antipsychotics. The 5-HT_{1A} receptors are also found to be linked to glucose homeostasis but the exact pathways are complex and no evidence suggests its involvement in antipsychotic-induced new-onset diabetes.

The involvement of leptin resistance in antipsychotic-induced new-onset diabetes is still studied. Leptin is released from adipocytes that are said to reduce appetite and stimulate catabolism of fat and inhibition of fat synthesis from adipocytes(35). Usually, an increased level of leptin is found in obese patients due to leptin resistance, similarly, research suggests that their levels were also elevated in patients using antipsychotics. The relevance and credibility of this hypothesis are questionable as the studies are done with a small number of patients taking antipsychotics.

Detection of glycemic intolerance

The detection of glycemic intolerance can be done by three different types of blood tests. These include fasting plasma glucose (FPG), two-hour oral glucose tolerance test (GTT), and glycated hemoglobin (HbA_{1c}).

Fasting plasma glucose (FPG)

After an overnight fast of 8 h, the blood sample is collected and the plasma glucose level between the range of 100-125 mg/dl (5.6-6.9 mmol/L) is indicative of IFG(36). As for diabetes, the IFG range should be greater or equal to 125 mg/dl. FPG is fast to perform but high variability can be observed.

Two- hour oral glucose tolerance test (OGTT)

The blood sample is collected before and after two hours of consuming about 75 mg of glucose. DM is detected if the plasma glucose (PG) range is higher or equal to 200 mg/dl. If the plasma glucose level is between 140-199 mg/dl, IGT can be diagnosed(36). The patient needs to include about 150 g of carbohydrate in their diet for 3 to 5 days and also should avoid drugs that can affect glucose tolerance (thiazides, steroids)(37). OGTT is more expensive than FGP, and the test is inconvenient due to restrictions of diet and certain medications.

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Glycated hemoglobin (HbA_{1c})

In HbA_{1c} the average blood glucose level of the past 2 to 3 months can be observed. HbA_{1c}range greater or equal to 6.5%(48 mmol/mol) indicates diabetes. Individuals with HbA_{1c}between 5.7%-6.4% (39 to 47 mmol/mol) have an increased risk of prediabetes or diabetes(38). The main advantage of HbA_{1c}over OGTT is the test can be repeated on any occasion as fasting is not necessary. HbA_{1c}range is also not affected by stress and thereby shows less variability HbA_{1c}should be measured based on National Glycohemoglobin Standardization Program(NGSP) certified method(39). Iron deficiency anemia, pregnancy, blood loss, or transfusion hemodialysis causes a false elevation in HbA_{1c}, resulting in limiting its use(40).

Gestational diabetesassociated with mental illness

A multicenter study to assess the association between gestational diabetes (GDM) and antipsychotics in pregnant patients with severe mental illness by Megan Galbally et al., reported that women with psychotic disorders were significantly at risk for developing GDM when compared with pregnant women without psychiatric illness(41). The study also reported that the use of specific antipsychotics such as risperidone ($P = 0.016$), clozapine ($P < 0.001$) and higher-dose quetiapine ($P = 0.029$) had increased risk of GDM. Another stud by Faruk Uguzalso reported similar data pertaining to the risk of GDM in pregnant patients using antipsychotics(42). A study conducted by Yoonyoung Parket al., on continuing the antipsychotics during early pregnancy reported that there is generally higher morbidity of GDM with longer use of antipsychotics(43). The risk of GDM in pregnant patients continuing on antipsychotics and withdrawing antipsychotics were compared and the study reported:4.8% and 4.5% for aripiprazole, 4.2% and 3.8% for ziprasidone, 7.1% and 4.1% for quetiapine, 6.4% and 4.1% for risperidone, and 12.0% and 4.7% for olanzapine users respectively. These issues with pregnant women must be taken seriously and early screening measures must be done to properly manage pregnant patients with mental illness.

Weight gain and insulin resistance – direct effects of antipsychotics

Insulin is a hormone secreted from the pancreas to regulate the glucose levels in our system. The increase or decrease of glucose levels is directly influenced by the daily food intake and its constituents. Surplus nutrition is a key factor in the development of insulin resistance. In adipocytes, uncontrolled lipolysis results in an increase in lipolysis results in the accumulation of specific lipid intermediates like diacylglycerol which causes muscle insulin

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resistance.The risk of developing pre-diabetes and diabetes mellitus markedly increases with an increase in Body weight and BMI. In patients prescribed with antipsychotics, there is a marked increase in body weight just in 6-8 weeks of treatment initiation(28). Antipsychotics induce weight gain and further glycemic resistance largely due to increased appetite and food uptake. The hypothesized reason for antipsychotic-induced weight gain is that these drugs affect the neurological and hormonal signals that regulate the feeding behavior and metabolism(44). The regulation of feeding behaviors such as the quantity of food one consumes and the feeling of satiety results from the coordination of hormonal and nervous signal inputs from the pancreas, gastrointestinal tract, and various parts of the central nervous system to the hypothalamus. The neuropeptides that are involved in these signaling pathways are largely affected by the presence of antipsychotic drugs. For example, the neurotransmitter 5 Hydroxy Tryptamine (5-HT) or serotonin acts in the HT2 receptor which stimulates anorexigenic proopiomelanocortin (POMC) neurons and decreases appetite, and dopamine is involved in reward pathways of appetite(34). Antipsychotics tend to affect the production and action of these neuropeptides which supposedly are prime targets in the management of various psychiatric disorders, but some antipsychotics inevitably create a concerning effect of meddling with the above-stated metabolic signaling pathways.

Another worrying causality of taking antipsychotics is that they are mainly sedatives and reduce voluntary physical movements which leads to reduced energy expenditure resulting in weight gain and glycemic intolerance.

The mechanisms underlying the development of insulin resistance are still studied and may occur at many levels of insulin signaling.

Effects on pancreatic islet beta cells

In subjects with glycemic intolerance, insulin secretion is gradually affected due to abnormalities in the beta-cell function which is a major determinant of the disease progression. Various clinical studies suggest that patients prescribed antipsychotics are 10 times more likely to experience diabetic ketoacidosis (DKA) as the first presentation of glycemic intolerance(45–47). This particularly develops due to the development of insulin resistance making the glucose reserve untouched leading to the metabolism of fats to make up for the energy requirements. The rate of development of DKA in patients with severe mental illness and a known history of diabetes mellitus and antipsychotics is 30 fold greater than the general population(48,49). DKA is a result of an extreme lack of insulin action which could have been caused by antipsychotics by affecting the pancreatic beta cells or other actions that

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disrupt the secretion of insulin. In animal studies, it was found that insulin secretion was impaired due to the use of olanzapine and clozapine. Antipsychotics affect the pancreatic insulin secretion when they produce their pharmacologic action on various receptors such as serotonergic, adrenergic, dopaminergic, and muscarinic receptors. The unintended glycemic intolerance can be mediated by the following activities of antipsychotics, blockade of D2 receptor can suppress the glucose-stimulated insulin release, blockade of 5-HT_{1a} and M3 receptors can dim the sensitivity of the pancreatic cells towards the fluctuation of blood glucose levels and blockade of adrenergic receptors increases basal insulin secretion(50).

Prevention of diabetes – methods of management

Before the patient gets full-blown diabetes mellitus, the glycemic tolerance develops gradually with the use of antipsychotics leading to an increase in blood sugar levels to prediabetic conditions and further progression if left unattended. Multiple Randomized controlled trials in the general population have demonstrated the impact of lifestyle preventive measures on preventing diabetes. However, very few studies have discussed the preventive strategies for diabetes in psychiatric patients(51). One of the key elements in preventing diabetes is a regular examination of blood sugar levels of patients prescribed with antipsychotics that have a higher risk of creating glycemic intolerance.A metanalytic comparative study of randomized control trials for analyzing the behavioral and lifestyle patterns that improve the metabolic status that was caused by antipsychotics(52). The meta-analysis reported significant weight loss and improved metabolic functions as an outcome of non-pharmacologic interventions. Managing schizophrenic patients with glycemic intolerance is more difficult compare to patients with other illnesses through lifestyle interventions(53–55). Although lifestyle measures are very essential to manage their weight and glucose reserves, there are no specific guidelines regarding the management protocols pertaining to the psychiatric population. But recommending the patients

Pharmacotherapy

Generally, glycemic intolerance can be managed only when itis identified, so regular screening tests for blood sugar levels must be recommended by the treating psychiatrists. There is no ideal way to prevent the development of glycemic intolerance in psychiatric patients. However, antipsychotics witha higher potential to affect the blood glucose levels can be avoided as best as possible and alternative agents can be recommended. In cases where it is not possible, the way to proceed would be to regularly monitor blood sugar levels and other

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symptoms. When the blood sugar levels rise to a concerning level, initially lifestyle modifications can be suggested and on levels that necessarily need pharmacologic agents, they must be prescribed. In the general population hypoglycemic drugs such as Metformin are used to reduce blood glucose levels, but the effects of those drugs are not extensively studied in populations using antipsychotics. However, a few studies have reported that metformin has shown a mean bodyweight reduction of 3.3kgs over 3-6 months, and an improvement in insulin resistance(56). Glucagon-like peptide – 1 (GLP-1) receptor agonists were also found to promote weight loss in diabetic patients(57). The American Diabetic Association recommends that psychiatric patients with diabetes must be managed by both the treating psychiatrist and a diabetologist. Various studies suggest that stopping the antipsychotic drug that caused the metabolic abnormality would possibly resolve diabetes is triggered. It is also equally important that a highly effective antipsychotic therapy must be followed preferably with an antipsychotic with less risk of creating glycemic intolerance to prevent psychotic relapse and psychological disorientation. Studies suggest that among the atypical antipsychotics' risperidone has the least propensity to cause glycemic intolerance. But no specific guidelines are available that recommend changing the antipsychotic therapy plans in psychiatric patients who develop diabetes. Since the implications of developing metabolic abnormalities such as significant weight gain, elevated blood sugar levels, or impaired glucose control are directly linked to morbidity and mortality, so it's essential to consider alternative antipsychotic drugs with fewerrisks.

Screening tactics for early detection of diabetes in people taking antipsychotics.

The relation between the use of various atypical antipsychotics such as olanzapine and clozapine are the development of glycemic intolerance is well known among psychiatrists. So, when such high-risk antipsychotics are prescribed to the patients it is recommended that their metabolic parameters such as blood glucose and cholesterol levels are monitored regularly. The most evident symptom that maybe associated with developing metabolic abnormalities is weight gain, which can be easily identified by the patient or can be assessed every time they come for a follow-up and prescription refills. Since the rise of metabolic diseases in the general population, psychiatric patients can be recommended to undergo metabolic investigations at least biannually. The clinically available methods for assessing the glycemic status arefasting and random blood sugar level tests, glycated hemoglobin levels (HbA_{1c}), and the two hours postprandial blood glucose levels. The ADA recommends the use of FBS and PPBS levels for screening diabetes mellitus(36). Explaining the risks of

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developing diabetes due to reduced physical activity and the use of antipsychotics to the patients or their caretakers is very essential to create and maintain awareness regarding the issue. The patients at risk can also be advised to obtain a glucometer to check for the rise in the blood sugar levels frequently.

CONCLUSION

Patients on antipsychotics for various psychiatric disorders should be considered as a high-risk population for developing glycemic intolerance and other cardiovascular disorders. Evidence also suggests that atypical antipsychotics are significantly related tothe development of diabetes and other metabolic disorders. Various mechanisms such as the interaction between the antipsychotic drug molecules and neuropeptides resulting in disarrangement in the hormonal and metabolic signals that control eating behaviors resulting in weight gain. Also, the nature of psychiatric disorders combined with antipsychotics is making it hard for psychiatric patients to engage in physical activities causing a sedentary lifestyle. Encouraging physical activity and other lifestyle modifications can improve the metabolic status of the patients. In addition, antipsychotics with lesser potential for weight gain and glycemic intolerance must be recommended as much as possible. Psychiatrists and diabetologists should devise appropriate therapeutic regimens to effectively manage the mental illness without disturbing the metabolic balance. Regular screen tests for diabetes mellitus and other CVDs must be recommended for early detection of any abnormalities, this must be followed strictly in patients prescribed with high-risk antipsychotics such as olanzapine or clozapine. Effective lifestyle and diet recommendations may prove to be helpful in managing drug-induced glycemic intolerance and weight gain.

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