Jurnal Ilmu Farmasi dan Farmasi Klinik
(Journal of Pharmaceutical Science and Clinical Pharmacy)
ISSN 1693-7899 (print) - 2716-3814 (online)
DOI: 10.31942/jiffk.v21i1.9529

Metabolic Syndrome and Side Effects of Atypical Antipsychotics in Schizophrenia: A Literature Review

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ABSTRACT: Atypical or second-generation antipsychotics are the most frequently prescribed antipsychotics due to their clinical efficacy and improved safety profile in the treatment of schizophrenia when compared to typical or first-generation antipsychotics. However, atypical antipsychotic drugs are associated with a high prevalence of adverse reactions, as well as side effects of metabolic syndrome. Schizophrenia is a chronic mental illness characterized by positive, negative, and cognitive dysfunctions. The objective of this review is to compare the impacts of atypical medication on MetS in patients with schizophrenia. A comprehensive analysis was conducted, including a literature review of the databases of Google Scholar, PubMed, and ScienceDirect for publications over the past decade. Seven articles were selected and reviewed for analysis. The analysis revealed that the use of atypical antipsychotics was associated with an increased risk of metabolic syndrome, while clozapine, olanzapine, and risperidone were associated with a higher risk of metabolic syndrome compared to other antipsychotics. The study also explores the mechanisms of metabolic syndrome, with a specific focus on the role of antipsychotics in disrupting glucose and lipid metabolism. This comprehensive study offers a nuanced understanding of the adverse effects of antipsychotic medications on the development of metabolic syndrome in individuals diagnosed with schizophrenia. This review revealed that the use of atypical antipsychotics in the treatment of schizophrenia can increase the risk of metabolic syndromes such as weight gain, dyslipidemia, hypertension, and diabetes. The primary limitation of this review is the high heterogeneity among studies, as they employed varying definitions of metabolic syndrome and included diverse sample characteristics.

Keywords: Metabolic Syndrome; Atypical Antipsychotic; Schizophrenia

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Submitted: 28-02-2025; Received in Revised Form: 06-05-2025; Accepted: 08-11-2025

INTRODUCTION

Metabolic syndrome, a constellation of disorders including obesity, dyslipidemia, and insulin resistance, has been identified in patients with schizophrenia for several years (Dobrowolski et al., 2022). One potential aetiology of this increased risk is the use of antipsychotic medications, particularly second-generation agents, which are associated with metabolic side effects such as weight gain, elevated blood sugar levels, and increased cholesterol (Keepers et al., 2020). Furthermore, the long-term use of antipsychotic medications in schizophrenia treatment contributes to the increased risk of metabolic syndrome (Dobrowolski et al., 2022). The prevalence of metabolic syndrome in patients treated with antipsychotics ranges from 37% to 65% (Akinola et al., 2023).

Research data from the Bali Provincial Mental Hospital indicates that the utilization of atypical antipsychotics in patients with metabolic syndrome is the most prevalent, accounting for 49.3% of cases. According to the National Health Service guidelines, the obesity component of metabolic syndrome is prioritized as the most significant. (Prabawa et al., 2019). According to the NCEP ATP III definition, metabolic syndrome is diagnosed when three or more of the following criteria are confirmed: blood pressure above 130/85 mmHg and a waist circumference larger than 102 cm for men or 88 cm for women. Additionally, the presence of elevated triglyceride levels (greater than 150 mg/dL), low-density lipoprotein levels (less than 40 mg/dL for men and less than 50 mg/dL for women), and fasting blood glucose levels (greater than 100 mg/dL) is indicative of metabolic syndrome (Cleeman, 2001).

Antipsychotics are medications that are prescribed to patients diagnosed with severe mental disorders, including schizophrenia, major depression, and bipolar disorder (Katzung & Trevor, 2020). However, these medications have the potential to induce metabolic syndrome (MetS), which can adversely affect life expectancy and adherence to treatment regimens (Akinola et al., 2023). Antipsychotic medications are generally categorized into two distinct classes: typical antipsychotics, also known as first-generation antipsychotics, and second-generation antipsychotics, also referred to as atypical antipsychotics. This classification is based on empirical evidence that atypical antipsychotics exhibit a low propensity to induce motor side effects (Chokhawala & Stevens, 2023). Typical antipsychotics have a long history of use and are effective in treating positive psychotic symptoms. However, these medications are frequently associated with significant motor side effects, including extrapyramidal symptoms. In contrast, antipsychotics of the atypical variety demonstrate a higher tolerance for extrapyramidal symptoms (Meltzer & Gadaleta, 2021). Nevertheless, they carry a heightened risk of metabolic syndrome, a condition characterized by weight gain, abnormal lipid levels, high blood pressure, and reduced glucose tolerance (Ardiansyah et al., 2024).

A study by Julaeha et al. (2021), a case report at Menur Mental Hospital, has identified the incidence of metabolic syndrome due to antipsychotics in Indonesia. The study stated that there is a relationship between weight gain, insulin resistance, and lipid profile abnormalities in patients with schizophrenia undergoing treatment with atypical antipsychotics. This observation aligns with the findings reported by Sona et al. (2020), which were conducted at the Mental Hospital in Padang among schizophrenia patients receiving antipsychotic therapy. It was observed that patients who received atypical antipsychotics as monotherapy or in combination experienced weight gain following the initiation of these medications. A systematic review by Akinola et al. (2023) stated that the

global prevalence of metabolic syndrome in patients treated with antipsychotics ranged from 37-65%. Conversely, the meta-analysis study conducted by Garrido-Torres et al. (2021) in patients who had never taken antipsychotics with a first psychotic episode identified a metabolic syndrome prevalence of 13.2%. Conversely, a cohort study comparing patients with a first episode of psychosis who were prescribed antipsychotic medications found that 60.70% of patients met at least one of the five parameters for metabolic syndrome NCEP ATP III (Garrido-Torres et al., 2022).

Individuals diagnosed with schizophrenia who are prescribed antipsychotic medications exhibit a higher prevalence of metabolic syndrome compared to the general population, particularly if they are administered atypical antipsychotics. A substantial body of research has demonstrated that the prevalence of metabolic syndrome in patients with schizophrenia who are prescribed atypical antipsychotics can range from 40% to 60%. This observation suggests a notable association between atypical antipsychotic drugs, such as olanzapine and clozapine, and metabolic syndrome, which can lead to the development of obesity, diabetes, and dyslipidemia (Carli et al., 2021). The present review aims to analyze the side effects of metabolic syndrome in the use of antipsychotics, atypical and identify the mechanisms involved and their influence on the condition, including obesity, dyslipidemia, hypertension, and diabetes..

METHODS

The type of research employed is qualitative research, utilizing literature methods. Review. Search through Google Scholar, PubMed and Science databases directly with a publication range of 2014-2024 using the keyword " metabolic syndrome ” OR “ MetS ” AND "Antipsychotic Atypical ” OR “ Second Generation Antipsychotics ” AND “ Schizophrenia ”

The inclusion criteria in this study were: (1) the article was research on metabolic syndrome effects in schizophrenia; (2) the article had a randomized controlled trial, experimental, or observational research design; (3) the Population research focused on adult patients (18-60 years) diagnosed with schizophrenia. Meanwhile, the exclusion criteria included (1) studies published more than five years ago; (2) studies that focused on populations other than patients with schizophrenia or patients not receiving atypical antipsychotics; (3) inappropriate study design, and (4) articles with incomplete or unextractable data.

The journals obtained were then reviewed based on their titles, abstracts, results, and conclusions, and compiled as a review of scientific literature studies. A Flow diagram of the search and selection strategies used in this systematic review is shown in Figure 1, following a systematic review and meta-analysis. Out of the 1754 articles, 491 were screened, and duplicates were removed based on pre-defined inclusion and exclusion criteria. Seven articles met the inclusion criteria for full-text screening, and 22 articles were excluded for various reasons.

This journal was written based on all journals that had been reviewed in their entirety. The data obtained from the research are summarised in Table 1. Results of tracing the incidence of metabolic syndrome impacts in schizophrenia individuals with schizophrenia undergoing atypical antipsychotic treatment.

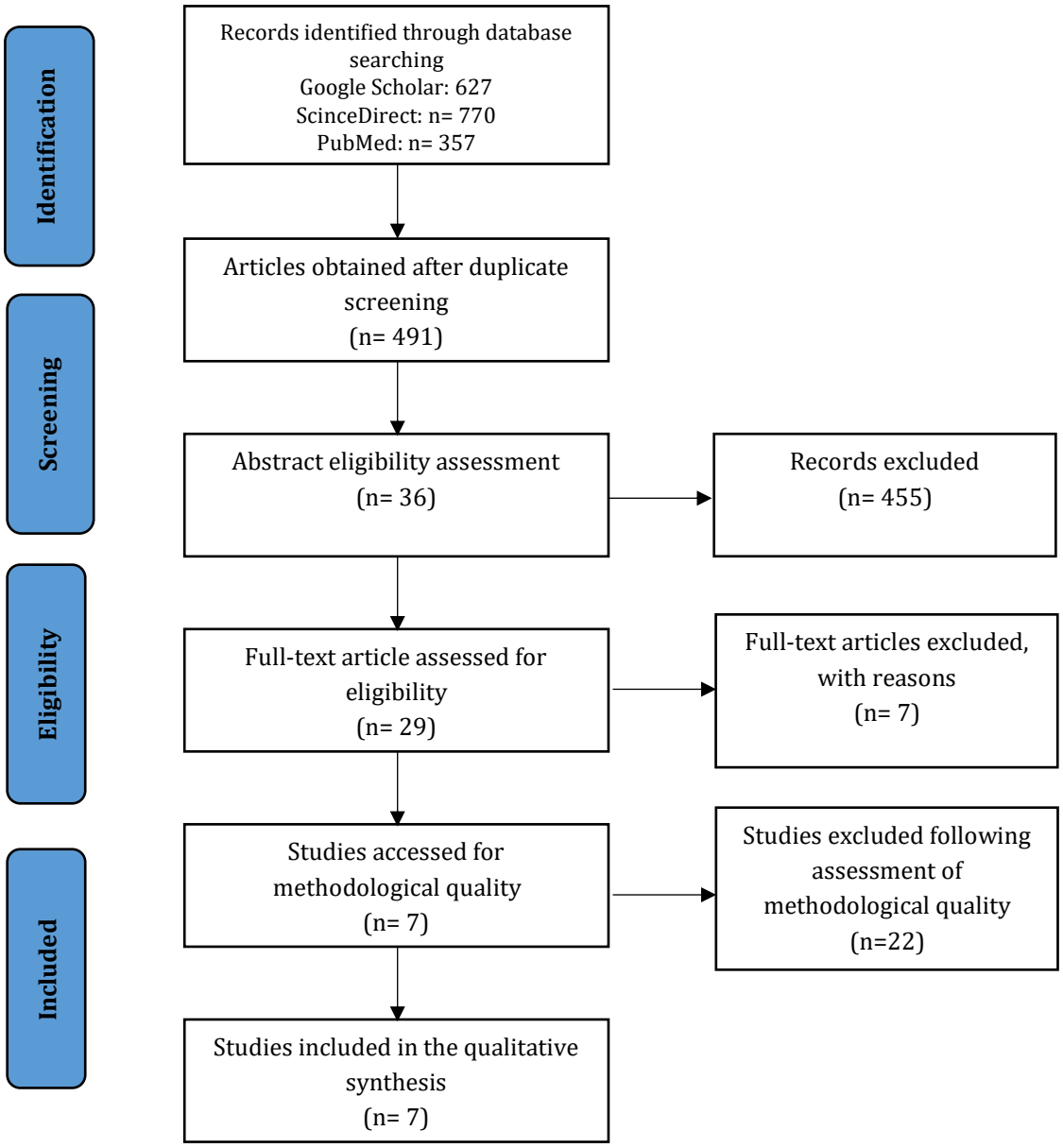

Figure 1. Flowchart of the search and selection strategy

RESULT AND DISCUSSION

The findings align with the research objectives regarding the effect of metabolic syndrome in schizophrenia patients receiving atypical antipsychotic therapy as shown in table 1.

Table 1. The research result of antypsychotic type

Authors	Method Study	Type Antipsychotics	Research result
(Abo Alrob et al., 2019)	Retrospective pre-post test Sample: 91	Olanzapine Clozapine Risperidone Quetiapine Aripiprazole Ziprasidone	37.4% of subjects experienced metabolic syndrome following six months of therapy, while 44% exhibited elevated systolic blood pressure, 54.9% demonstrated improvements in triglyceride levels, and 31.9% displayed disturbances in glucose levels.
(Makary et al., 2023)	*Cross Sectional* 2 groups (control and treatment) Sample: 72 per group	Risperidone Olanzapine Quetiapine Aripiprazole	In the treated group with atypical antipsychotics, 22.22% suffer from type 2 diabetes, compared with 2.53% in the control group. Average patients show the occurrence of obesity after treatment with antipsychotic atypical antipsychotics, which is a predictor of the occurrence of metabolic side effects.
(Beyene et al., 2024)	*Cross Sectional* Sample: 271	Risperidone and Olanzapine	Prevalence syndrome metabolic by 35.8%, of which 70.8% have improved circumference waist and 42.8% low HDL-C levels
(Ardiansyah et al., 2024)	*Prospective Cohort* Sample: 30	Risperidone and Clozapine	After two months of consuming an atypical antipsychotic, there was an improvement in body weight and blood glucose fast.
(Herlina et al., 2021)	Retrospective with consecutive *sampling* Sample: 80	Risperidone and Clozapine	After 4 weeks use of risperidone and clozapine on body weight of subjects experiencing improvement 0.3 kg
(Prabawa et al., 2019)	Descriptive *cross sectional* analysis Sample: 245	No mentioned	Syndrome parameter profile metabolic improvement happens after consuming atypical antipsychotics, especially in conditions of obesity and dyslipidemia.
(Riawan et al., 2022)	*Cohort Prospective pre-post test* Sample: 361	Risperidone	If compared with *pretest* administration, antipsychotic risperidone- based regimens showed the occurrence of worsening conditions, obesity, hypertension, cholesterol, and diabetes mellitus after consuming antipsychotics

Most studies have shown the effect of antipsychotic administration on the development of metabolic syndrome, which is measured by weight gain, the effect on blood glucose and lipid profiles of schizophrenia patients who use antipsychotic therapy. A cohort

study, prospective in South Sulawesi, found that Schizophrenia patients undergoing treatment with antipsychotics experienced increased body weight and fasting blood glucose in the second week after treatment with this antipsychotic—risperidone and clozapine (Ardiansyah et al., 2024).

Herlina et al. (2021), a retrospective study of 80 patients who were hospitalized with schizophrenia with atypical antipsychotic treatment for 1 month, showed weight gain, especially in patients who were given a combination of atypical antipsychotics, namely risperidone and clozapine. Meanwhile, Prabawa et al. (2019) described the proportion of incidents of metabolic syndrome side effects using the National Cholesterol Education Program Adult Treatment Panel III parameters. They found that 87.3% of patients were obese after using antipsychotics.

Antipsychotic Atypical with Metabolic Syndrome

Second-generation antipsychotics, including risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone, and clozapine, have been shown to demonstrate higher affinity for serotonin receptors compared to dopamine receptors. These medications have been associated with adverse effects, such as weight gain and lipid metabolism. (Stahl, 2013). Clozapine, a prominent example of a second-generation antipsychotic, has been observed to lack extrapyramidal side effects (Keepers et al., 2020). Aripiprazole, a second-generation antipsychotic agent, displays partial agonist activity at dopamine D2 receptors. This distinct pharmacological profile contributes to the distinct side effect profile of these medications. Aripiprazole has been shown to have a low risk of extrapyramidal side effects. (Huhn et al., 2019).

The relationship between atypical or second-generation antipsychotic use and metabolic syndrome has become a significant concern in psychiatric research. Various literature sources, such as (Carli et al., 2021; Doménech-Matamoros, 2020; Lin et al., 2023; Pu et al., 2021) have shown the important contribution of severe mental disorders, including schizophrenia, major depressive disorder, and bipolar disorder, in the emergence of metabolic syndrome and degenerative diseases associated with hypertension, dyslipidemia, and diabetes. Many factors can contribute to metabolic syndrome, including the duration of treatment, dosage of medication, diet, lifestyle (such as activity level, physical activity, and smoking habits), and non-pharmacological interventions, as well as the patient's genetic predisposition factors (Lin et al., 2023).

Cross-sectional research in Ethiopia showed that schizophrenia patients treated with atypical antipsychotics (second generation antipsychotics) on the prevalence of metabolic syndrome occurred in 35.8% of female patients with olanzapine use, which is a predictor of metabolic syndrome (Beyene et al., 2024). Clinical trial results Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) involving more than 600 patients with schizophrenia showed that the prevalence of metabolic syndrome for olanzapine increased over 3 months from a baseline of 34.8% to 43.9%, CATIE investigators also reported that 3 months of olanzapine and quetiapine were associated with the most significant mean increase in waist circumference (0.7 inches), followed by risperidone (0.4 inches). Olanzapine was also associated with changes in fasting triglyceride levels at 3 months (greater than 21.5 mg/dL). Weight gain was greater with olanzapine (0.9 kg/month) compared with quetiapine or risperidone (0.2 kg/month) (Riordan et al., 2011).

The mechanisms underlying the association of metabolic syndrome with the use of second-generation antipsychotics are complex and involve various factors, such as

pharmacological effects of drugs on the central nervous system and peripheral metabolism. Although the exact mechanism is not fully understood, several factors contribute significantly to the side effects of metabolic syndrome, including the presence of impaired glucose metabolism, characterised by insulin resistance and pancreatic beta cell dysfunction (Singh et al., 2019). Antipsychotics can interfere with cell sensitivity to insulin, making it difficult for blood glucose to enter cells. As a result, this can lead to increased appetite. The use of antipsychotics can also affect the satiety centre in the brain, causing patients to feel hungrier and consume more food. In addition, there are changes in the lipid profile, such as increased triglycerides, because antipsychotics can increase triglyceride production in the liver, and the effects of antipsychotic use also affect excessive (Carli et al., 2021). The mechanism of side effects of antipsychotics with metabolic syndrome has been explained by Singh et al. (2019), as shown in Figure 2.

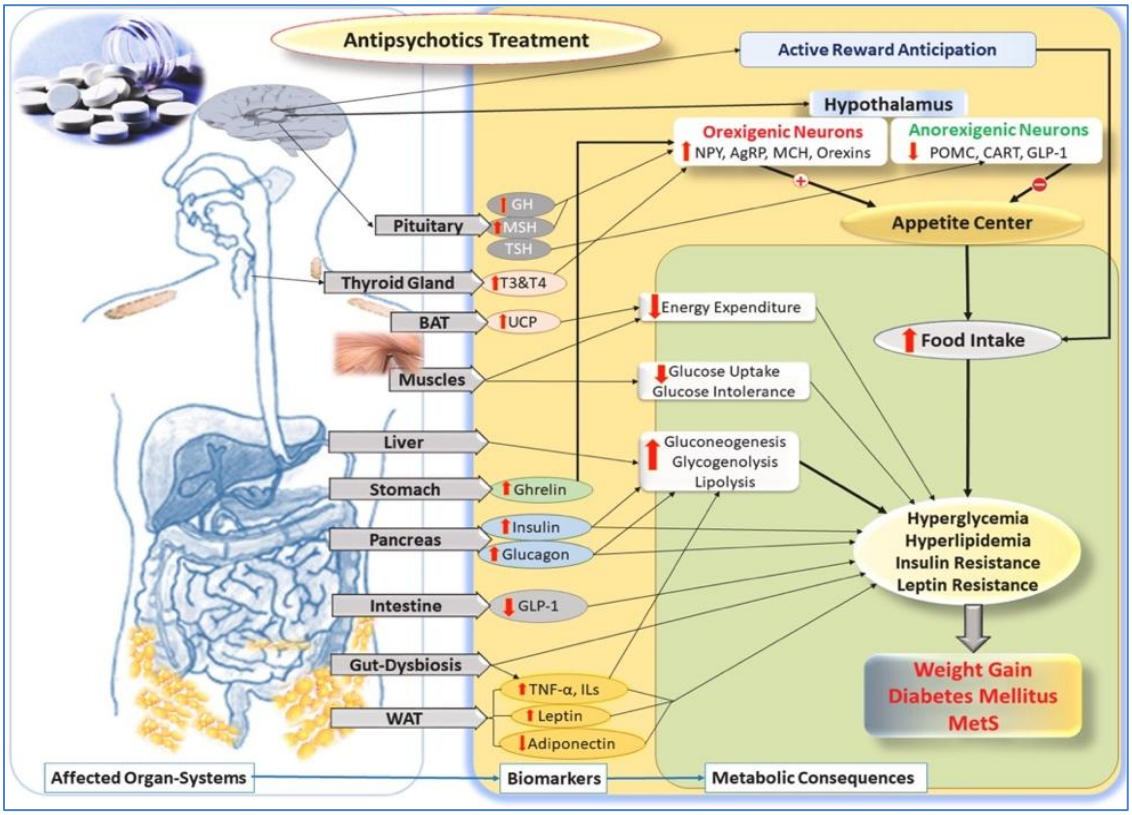

Figure 2. Mechanism of the Relationship between Antipsychotics and Metabolic Syndrome (Singh et al., 2019)

Several studies have shown that antipsychotics can decrease IRS-1 protein expression in insulin target tissues, reducing the amount of substrate available for insulin signalling (J. Chen et al., 2017). Antipsychotics can activate various kinases (e.g. JNK, ERK, PKC), which then phosphorylate IRS-1 at serine and threonine residues. Phosphorylation at these residues often results in inhibition of insulin signalling, rather than activation. Serine/threonine phosphorylation can reduce the ability of IRS-1 to interact with the Insulin Receptor (IR) and activate downstream pathways (Arinami et al., 2024; Chen et al., 2021; Tanti & Jager, 2009).

Atypical antipsychotics such as clozapine, olanzapine and risperidone appear to be involved in the development of MetS. (Pu et al., 2021). In clinical practice, among atypical antipsychotics, olanzapine and clozapine are associated with the highest risk of MetS, while quetiapine, risperidone, asenapine, and amisulpride cause moderate changes (Mazereel et al., 2020). Weight gain is associated with the use of clozapine and olanzapine, while increased prolactin levels are often associated with risperidone use (Meltzer & Gadaleta, 2021). Mazereel et al. (2020 in their analysis stated that there is an impact of antipsychotic treatment on obesity and metabolic disorders. The differences in the side effects of typical and atypical antipsychotics that can cause metabolic syndrome disorders can be seen in the side effects of weight gain, hyperlipidemia and glucose abnormalities, as seen in **Table II.**

Table II. Differences in side effects of metabolic syndrome components from various types of antipsychotics, atypical (Mazereel et al., 2020)

Drug name / Effect to	Improvement Weight	Hyperlipidemia	Abnormality Glucose
Antipsychotics Generation Second (APG-2 / Antipsychotic Atypical)			
Aripiprazole	+	+	+
Clozapine	+++	+++	+++
Olanzapine	+++	+++	+++
Quetiapine	++	+++	++
Risperidone	++	+	++
Paliperidone	++	++	+

Description: effects indicated as extremely high (++++), high (+++), average (++), low (+), very uncommon (+/−)

Obesity, a condition marked by an excessive buildup of fat tissue, has been noted in individuals using SGAs (second-generation antipsychotics). The underlying mechanism of this phenomenon involves the impact of these medications on weight gain, as evidenced by alterations in abdominal circumference and visceral fat levels (Makary et al., 2023). Antipsychotics are known to increase appetite, leading to weight gain. Antipsychotics are known to increase appetite, leading to weight gain. The metabolic consequences of atypical antipsychotic drugs vary widely with respect to the receptor pharmacology (Riordan et al., 2011). The two medications that appear to have the most significant impact on body weight are Olanzapine and Clozapine, due to their strong affinity for the 5-HT2C and histamine H1 receptors.

Atypical antipsychotics, through their pharmacological actions as antagonists at 5-HT2C and H1 receptors (as well as other receptors such as D2, 5-HT2A, alpha-adrenergic, and muscarinic), may interfere with the normal regulation of appetite, glucose, and lipid metabolism. The antagonistic effects at 5-HT2C and H1 in particular are believed to play a significant role in the metabolic side effects frequently observed (Singh et al., 2019). Weight gain primarily through increased appetite due to 5-HT2C and H1 blockade (Doménech-Matamoros, 2020; Herlina et al., 2021). Insulin resistance and type 2 diabetes through disruption of the insulin signalling pathway influenced by 5-HT2C and possibly also H1, and secondarily due to weight gain (Chen et al., 2017; Mazereel et al., 2020). Meanwhile, dyslipidemia is due to changes in blood lipid levels (increased triglycerides, decreased

HDL), which can be influenced by direct disturbances in lipid metabolism and indirectly by weight gain (Chen et al., 2021; Pu et al., 2021).

Hypertension is a common issue among individuals receiving extended antipsychotic treatment, frequently resulting from metabolic syndrome. A retrospective analysis of inpatients with schizophrenia showed that olanzapine, risperidone, and ziprasidone increased systolic blood pressure at different points during nine vital sign assessments conducted within three days after treatment began (Saklayen, 2018). Second-generation antipsychotics have been demonstrated to affect glucose tolerance adversely. These mechanisms may occur in various physiological systems, including the liver, pancreatic beta cells, and the autonomic nervous system (Rice & Ramtekkar, 2020). The possible role of receptors in these synergistic influences encompasses the enhancement of 5-HT2C-related effects on food consumption by D2 receptor antagonists and the disinhibition of prolactin regulatory processes, which impact glucose metabolism (C. Y.-A. Chen et al., 2021).

Management of Metabolic Syndrome Due to Antipsychotics

Early detection of metabolic syndrome enables the implementation of a comprehensive, interdisciplinary management approach to control risk factors that compromise organ function and cardiovascular health. This metabolic syndrome develops gradually over several years, beginning with the emergence of excess weight and obesity, later accompanied by additional elements of the metabolic syndrome (Saklayen, 2018). All individuals with metabolic syndrome must be advised to make lifestyle changes. In many situations, they are provided with treatment options to assist in weight reduction and manage the key elements of metabolic syndrome, including the management of hypertension, dyslipidemia, atherogenic conditions, and diabetes. (Dobrowolski et al., 2022).

In individuals with obesity and prediabetes, the primary goal of treatment should be to reduce weight by 5–7%. For those with obesity and diabetes, the aim is to attain a weight loss of at least 7–15%. In addition to dietary changes, increasing physical activity is recommended. The recommended physical activity should specify its type, intensity, frequency, and duration (Howard, 2006). The primary objective of treatment in patients with diabetes is to lower the risk of long-term complications, which includes cardiovascular risk. It is crucial to reach target levels for glycemia, blood pressure, lipoprotein, low-density lipoprotein (LDL), non-HDL cholesterol, and body weight, as these factors are essential components of metabolic syndrome. The use of medications proven to be effective in lowering cardiovascular risk and body weight is also suggested. For patients with hypertension and metabolic syndrome, non-pharmacological interventions focusing on significant lifestyle changes should be implemented. These changes involve reducing body weight, reducing salt consumption, and increasing physical activity (Dobrowolski et al., 2022).

CONCLUSION

Our analysis found that atypical antipsychotics may raise the risk of metabolic disorders like weight gain, hypertension, diabetes, and dyslipidemia. Atypical antipsychotics are linked to metabolic syndrome, although all antipsychotic patients should be monitored. Atypical, with sufficient dose adjustment, avoiding multiple antipsychotic combinations, and assessing body weight, waist circumference, blood pressure, and blood sugar to

prevent metabolic syndrome adverse effects. This literature review focused on metabolic syndrome and atypical antipsychotic-related metabolic adverse events in schizophrenia patients. Thus, our literature search and data analysis did not examine non-metabolic adverse events, including oesophageal consequences. In this study, we know little about the timing of non-metabolic adverse events and how drug combinations affect them. More research is needed to understand the full range of atypical antipsychotic side effects, including temporal features and medication interactions.

AUTHOR CONTRIBUTION

ANP: research design development, analysis, and interpretation of results, draft manuscript preparation.
Y: design the study, revise the manuscript, edit the manuscript for critical intellectual.

CONFLICT OF INTEREST (If any)

None to declare

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