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Metabolic Complications of Antipsychotic Treatment in Newly Diagnosed Psychotic and Mood Disorders: A Case-Control Study on Dyslipidemia and Hyperglycemia

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ABSTRACT

Objective: This study aimed to investigate the association between statin use and metabolic disorders when prescribed either as adjunctive therapy to antipsychotics or as monotherapy in newly diagnosed individuals with schizophrenia and other psychiatric disorders involving mood disturbances or psychosis.

Methods and Materials: A matched case–control analysis was conducted using electronic medical records and files from Jordan University Hospital, King Abdullah University Hospital, and the National Center for Mental Health. Eligible patients were 20–55 years old, diagnosed with schizophrenia, bipolar disorder, or affective psychosis, and treated continuously for 4–6 months with the same antipsychotic or statin. Individuals with pre-existing medical conditions affecting metabolism (e.g., diabetes, endocrine or renal disorders, cardiovascular disease) were excluded. For each case presenting metabolic symptoms (dyslipidemia or hyperglycemia), a control participant was selected, matched by age, sex, psychiatric diagnosis, and metabolic profile. Conditional logistic regression was applied to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each medication.

Findings: The analysis included 986 cases with metabolic syndrome and 1,678 matched controls. The use of olanzapine (OR = 4.42, 95% CI: 3.73–5.23) and risperidone (OR = 5.17, 95% CI: 4.15–6.44) was strongly associated with a higher risk of metabolic syndrome, whereas quetiapine posed a minimal risk. Aripiprazole significantly reduced risk (OR = 0.081, 95% CI: 0.04–0.16). Statins also demonstrated a protective effect (OR = 0.27, 95% CI: 0.18–0.40).

Conclusion: Findings suggest that statins may mitigate metabolic side effects in patients undergoing antipsychotic therapy. Importantly, mood disorder patients receiving statins did not develop metabolic complications, highlighting their potential role in improving both psychiatric and metabolic outcomes.

Keywords: statin, metabolic disorder, hyperlipidemia, hyperglycemia, anti-psychotic.

Introduction

Metabolic syndrome is characterized as “a cluster of the most dangerous heart attack and cardiovascular disease risk factors,” according to the International Federation for Diabetes (IDF) (Alberti, 2020).

Dyslipidemia and hyperglycemia are listed as the primary factors of metabolic syndrome, which are characterized by elevated triglycerides (> 150 mg/dL) and fasting glucose (> 110 mg/dL). Specifically, abnormal increases in fasting glucose are indicative of diabetic type 2 diabetes, while elevated triglycerides are considered the primary risk factor for cardiovascular disease (Sherling & Hennekens, 2017)

However, the primary role of insulin in the metabolism process characterizes a metabolic disorder as insulin resistance, characterized by a reduction in insulin sensitivity at the cellular level in hepatocytes,

muscle cells, and adipocytes due to a dysfunctional insulin signaling pathway, damage to β-cells, or elevated levels of free fatty acid (Kahn, 2014).

The occurrence of psychotic disorders has markedly risen in recent years, primarily in the Middle East region, as a result of global upheavals such as wars, economic crises, and natural disasters. The ongoing crises and the COVID pandemic have particularly contributed to this surge (Refugees, 2021). Research conducted in Jordan reveals that a substantial proportion of individuals diagnosed with COVID-19 encounter moderate to severe psychotic symptoms, with more than 50% of them being afflicted. Furthermore, nearly 33% of patients encounter manifestations of anxiousness (Mahmoud Alali, 2023).

In addition, the Global Burden of Disease report in 2017 found that the prevalence of major depressive disorder (MDD) in the Jordanian population was assessed to be 2.5%, while the prevalence of schizophrenia was estimated to be 0.2% and the prevalence of bipolar disorder was estimated to be 0.8% (GBD, 2018).

Antipsychotic drugs are frequently prescribed for the treatment of mental illnesses or psychotic conditions, including schizophrenia, anxiety, mood disorders, bipolar disorders, obsessive-compulsive disorders, and delirium disorders.

Antipsychotic medications, commonly used to treat agitation, dementia, autism spectrum disorder, insomnia, chronic pain, and migraines, have shown a substantial increase in prescription rates in both developing and high-income nations.

Researchers are focusing on assessing the risks and effects of antipsychotics (Verdoux et. al., 2010). According to Tandon et al., second-generation 'atypical' antipsychotics have a lower risk of extrapyramidal adverse effects and fewer side effects on neuromuscular and sexual activity compared to first-generation antipsychotics (Tandon, 2008); other studies have proven them to be risk factors for cardiovascular disorders, diabetes, and obesity. Therefore, it has a higher risk of metabolic disorder (Kaur, 2014); accordingly, based on Akinola PS et al., about 37%–63% of patients who take antipsychotics will have metabolic disorders, which include cholesterol and triglyceride metabolism disorder (dyslipidemia) and glucose homeostasis dysregulation (diabetes due to insulin resistance) (Akinola, 2023).

Based on a study carried out by A. Zarina Kraal et al. (2017), females have a higher likelihood than males of encountering the consequences and influence of antipsychotic medications. Additionally, the likelihood of being susceptible to a specific condition or disease increases with age, regardless of gender. Ziprasidone, lurasidone, cariprazine, aripiprazole, brexpiprazole, and amisulpride are safer and associated with fewer metabolic issues compared to olanzapine, clozapine, and risperidone, which have a higher incidence of metabolic problems (Correll, 2020; Pillinger, 2020), particularly during long-term treatment lasting 4 to 6 months (Zhang, 2013)

Many reviews have proven the effects of antipsychotics on the metabolic process. Accordingly, side effects occur within 4 weeks of treatment, as noted by Emily Eyles et al., and worsen over a longer duration of therapy (Eyles, 2023). Most of these reviews based their results on assessing the measurements of blood pressure, weight, HDL-C, triglycerides, HbA1c, waist circumference, and fasting plasma glucose.

Many people routinely use statins to prevent lipid-related cardiovascular disorders by lowering their TC, LDL, and TG concentrations. Moreover, statins function as anti-inflammatory agents (Zhang, 2019) and antioxidants (Khan, 2018), making them suitable and effective for certain neuropsychiatric disorders (Wang, 2019). Lots of epidemiological and experimental studies have assessed and substantiated the impact of statins on numerous neuropsychiatric illnesses. Statins have an effective role in managing the negative symptoms of schizophrenia. Especially when used with lipophilic statins with sufficient duration and dose (Li, 2020a, 2020b) (Wang, 2020a). More than ever, statins have a positive impact on bipolar disorder symptoms (Li, 2020c; Wang, 2020a), mood disorder abnormalities (Zhang, 2019), and reducing anxiety (Avan, 2021).

However, lipophilic statins (such as simvastatin) have greater protective and improvement effects than hydrophilic statins in cases of psychological disorders due to their better brain penetration (Li, 2020a, 2020b).In addition to its constructive role in the management of cardiovascular risk factors in patients who undergo second-generation antipsychotics (SGAs), Statins were effective in improving many psychological symptoms when used in combination with antipsychotics,

compared to using antipsychotics alone (Wang, 2020a, 2020b).

For decades, in lots of studies, research has proven the relation between metabolic disorder and antipsychotic use (Gao, 2019; Liu, 2019; Newcomer, 2018). More importantly, they clarified the impact of antipsychotics on causing dyslipidemia and hyperglycemia.

However, this study examined the effects of statins on metabolic disorders in Jordanians newly diagnosed with schizophrenia or other psychotic disorders and mood disorders, either as an alternative to antipsychotics or in combination with them.

Methods and Materials

Study Design and Participants

The study design is an observational, retrospective, multicenter case-control study involving two groups: the control group, comprising psychiatric individuals without symptoms of metabolic disorders (comparison subjects), and the case group, which includes subjects who meet the selection criteria outlined in the study population section. However, we defined the index date as the period from the end of March 2023 to the end of March 2024.

Al Hussien Bin Talal University and the Ministry of Health in Jordan (code number 1352) ethically approved the study procedures. We analyzed the electronic medical records of all drowning cases in inpatient and outpatient clinics at Jordan University Hospital, King Abdullah University Hospital, and the National Center for Mental Health in Jordan from March 2023 to March 2024.

Inclusion and exclusion criteria: The study participants were psychiatric patients who had undergone continuous anti-psychotic therapy for at least 4 months and up to 6 months with the same anti-psychotic, having completed therapy two months before the index date. The samples were sorted into two groups, the first being the case group (subjects), which was identified based on medical laboratory records according to which it was proven that there were indicators of metabolic disorders (TG > 150 mmHg, HDL< 40 mg/dL in men and <50 mg/dL in women, and fasting glucose >110 mg/dL). The other group was the control, which included participants who did not have any symptoms of metabolic disorder. The inclusion criteria for the participants in two groups are as follows: Participants must be between the ages of 20 and 55, and they must suffer from one or more of the following psychological disorders: Schizophrenia, mood disorders, bipolar disorder (BD), and any affective psychosis or psychological symptom that was treated with antipsychotics for continuously between 4 and 6 months of therapy, all participants in two groups who had any history of chronic disease, those treated for any medical condition, who had a history of diabetes, endocrine disorder, or hormonal dysregulation, who had a history of obesity or eating problems, who were taking any medications known to affect metabolic activity like beta blockers, niacin, thiazide, thiazolidinedione agents, immunosuppressive drugs, steroids, or antiepileptics, and who had cardiac or renal diseases were excluded from this study. This study also excluded all patients who received first-generation antipsychotics, received two types of antipsychotics, did not complete the therapy, or received it discontinuously.

Recruitment: The research team recruited 2,664 electronic records and file records, matched 986 selected cases of metabolic disorder with 1,678 comparison subjects, and collected data by reviewing the electronic records and file records of outpatients in psychiatric clinics within the mentioned centers. Eligibility for both groups was determined based on the inclusion and exclusion criteria. The research team scrutinized the psychiatric clinic's records for eight months before the index date, identified the relevant records for this study, linked them to the laboratory records, selected 986 records (subjects) for the case group, and selected 1678 suitable records (comparison subjects) for the control group. Laboratory test results and other demographic information were collected and prepared for statistical analysis.

Data Analysis

A case-control analysis was conducted using SPSS version 25. The descriptive measurements consisted of frequencies and percentages for all categorical variables, and the mean (± standard deviation) for continuous measures. Conditional logistic regression was used to model the influence of second-generation antipsychotics (SGAs) and the role of statins on metabolic processes. The findings are reported as odds ratios along with 95% confidence intervals (95% CIs).

Findings and Results

When it came to compression, males dominated females by a margin of 62.99%, while the majority of subjects with metabolic abnormalities were female (68.96%). Participants with metabolic problems had a mean age of 41.4 years (SD = 11.2), while comparison participants had a mean age of 40.9 years (SD = 15.4). The two groups were well matched in terms of age.

Schizophrenia is the most common case in both groups, reaching 559 (56.69%) patients of subjects and 346 (20.61%) patients of comparison subjects, followed by bipolar, with 319 (32.35%) bipolar patients of subjects, 367 (24.92%) bipolar patients of comparison subjects, 73 (7.40%) mood disorders patients of subjects, and 60 (3.57%) mood disorders patients of comparison subjects (Table 1).

Table 1

Subjects with Psychotic Disorders And Metabolic Disorders, Along With Matched Comparison Subjects, Have the Following Characteristics:

	Subjects with metabolic disorders		Comparison subjects	
	(N = 986)	(%)	(N =1678)	(%)
Male	306	31.03	1057	62.99
Female	680	68.96	621	37.00
schizophrenia	559	56.69	346	20.61
Bipolar	319	32.35	294	17.52
Mood disorder	73	7.40	60	3.57
Other affective psychosis	35	3.54	978	58.28

The majority of subjects (59.83%) received olanzapine as their antipsychotic therapy, followed by risperidone (31.84%), statin (3.24%), quetiapine (1.62%), and aripiprazole (1.01%). In contrast, quetiapine (37.12%) was the most common medication among the comparison subjects. This was followed by Olanzapine (25.20%), Statin (10.78%), Risperidone (8.28%), and Aripiprazole (5.48%).

In the conditional logistic regression model, people who took olanzapine and risperidone had a much higher chance of developing a metabolic disorder than people who took other antipsychotic drugs. On the other hand, people who took quetiapine, statins, and aripiprazole had a much lower chance of developing a metabolic disorder (Table 2).

Table 2

The Relationship Between the Treatment of Metabolic Disorders and the Use of Antipsychotic Medication

	Subjects with metabolism disorder (N = 986) (%)		Comparison subjects (N =1678) (%)		Odds ratio	95% CI	Significance level
Olanzapine	590	59.83	423	25.20	4.42	3.73 – 5.23	P<0.0001
Risperidone	314	31.84	139	8.28	5.17	4.15 – 6.44	P<0.0001
Quetiapine	16	1.62	623	37.12	0.02	0.01 – 0.04	P<0.0001
Aripiprazole	10	1.01	92	5.48	0.08	0.04 – 0.16	P<0.0001
Statins (simvastatin & atorvastatin)	32	3.24	181	10.78	0.27	0.18 – 0.40	P<0.0001
No medication	24	2.43	220	13.11	0.16	0.10 – 0.25	P<0.0001

Discussion and Conclusion

Metabolic disorders have been identified as a significant risk factor for early death, increased mortality, cardiovascular disease, and diabetes problems in psychiatric patients treated with second-generation antipsychotics. Studies in Jordan have focused on examining the relationship between metabolic disorders and the use of anti-psychotics, leading to the confirmation by AboAlrob O et al. of a positive correlation between the use of second-generation anti-psychotics and metabolic disorders in schizophrenic and bipolar patients (Osama Abo Alrob, 2019). This outcome is consistent with the findings attained by

the current study. However, due to statins' role as anti-inflammatory agents and the strong connection

between mental illness and inflammation, numerous theoretical frameworks and clinical studies have demonstrated the efficacy of statins in mitigating or averting metabolic side effects. This has established statins as augmentation treatments, preventative tactics, or substitute therapies for anti-psychotics. Few clinical trials have addressed the psychotic impact of statins (Avan et al., 2021; Ikuo Nomura, 2017; C., 2018). The current study provides an analytical comparison to evaluate the psychotic role of statins and their relation to metabolic disorders in cases of schizophrenia and bipolar or mood disorders.

According to Zarina Kraal (2017), females who have undergone antipsychotics are more susceptible to metabolic disorders than males, and this corresponds to the gender prevalence in the current study. Therefore, gender is a risk factor for developing metabolic disorders in cases of antipsychotic use.

In a recent study, all subjects who had received olanzapine or risperidone were most susceptible to developing metabolic disorders (OR olanzapine: 4.42, risperidone: 5.17). Olanzapine is the most widely used in schizophrenic subjects; it was considered the best among the anti-psychotics and the most effective for schizophrenia patients, despite its side effects on metabolic processes. In this study, it was noted that more than half of the schizophrenia subjects (59.83%) were treated with olanzapine, based on (Rong li, 2020).

Using olanzapine continuously and regularly between 4 and 24 weeks leads to a metabolic disorder in which the level of HDL and glucose significantly rises, followed by risperidone, which is considered the best choice of treatment for bipolar patients despite the risk of an increase in TG levels above the normal range (Vancampfort D, 2015). Duncan, Woolson, Hamer, & Dunlop (2009). These findings are consistent with the current study, which reported that 59.83% of subjects who underwent olanzapine experienced an increase in HDL above the normal level, and 34.8% had an increased level of fasting glucose above the normal level. Also, 31% of the patients who took risperidone had a raised TG level.

According to a recent study, quetiapine was found to be the safest antipsychotic when it came to metabolism. Of the people who took the comparison drug, 37.12% used quetiapine and didn't experience any issues with their metabolic factors (TG, HDL, or fasting glucose); however, individuals who took statins were less likely to develop a metabolic disorder than those who took other medications. Furthermore, the odds of metabolic disorder were the lowest in cases of quetiapine use compared with other antipsychotics (Table 2).

Researchers considered statins a suitable option for controlling mood disorder symptoms (Avan, 2021; Zhang, 2019). In the current study, olanzapine and quetiapine were used to treat all mood disorder subjects, whereas statins (simvastatin) were used to treat 3.27 percent of mood disorder cases in comparison subjects. Therefore, statins are the most effective treatment for mood disorder cases.

This study demonstrated the role and positive effects of statins on psychological symptoms, acting as supportive and alternative medications to anti-psychotics, making them suitable for mood disorders and positive psychosis cases.

The current study confirms the adverse effects of olanzapine and risperidone on metabolic processes, in line with previous studies. This study investigated the presence of statin compounds in psychotherapy and their impact on metabolic activity in psychological cases. Therefore, preliminary studies have proven the positive effects of simvastatin in mood disorders, necessitating future experimental studies to investigate the role of statins more precisely.

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Declaration of Interest

The authors of this article declared no conflict of interest.

Ethical Considerations

The study protocol adhered to the principles outlined in the Declaration of Helsinki, which provides guidelines for ethical research involving human participants. Ethical considerations in this study included the fact that participation was entirely optional. This research was funded and approved by Al Hussein Bin Talal University (number # 189/2023).

Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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Authors' Contributions

All authors equally contribute to this study.

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