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Cardiovascular risk associated with antipsychotic treatment in a real-world cohort

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Abstract

Objective: To evaluate cardiovascular (CV) risk associated with long-term antipsychotic treatment in a real-world cohort.

Methods: A cross-sectional study was conducted in 75 patients diagnosed with schizophrenia or schizoaffective disorder under antipsychotic therapy for more than five years. Clinical parameters including blood pressure, lipid profile, glucose, HbA1c and C-reactive protein were measured. CV risk was categorized according to IAS-AGLA criteria.

Results: The mean age was 47 ± 15 years, with 47% females. Mean cholesterol was 195.5 ± 40 mg/dL, LDL 118.4 ± 33.8 mg/dL, HDL 49.0 ± 17.2 mg/dL, and triglycerides 151.7 ± 75.4 mg/dL. Ten-year CV risk was >10% in 28% of patients. Sixteen percent required lipid-lowering therapy and 14.5% antihypertensive treatment. Patients receiving GABAergic drugs (valproate, escitalopram, topiramate, diazepam) showed a protective effect against high CV risk (OR=17, p=0.049).

Conclusion: Nearly one-third of patients under chronic antipsychotic therapy demonstrated elevated CV risk. These results reinforce the importance of preventive strategies, structured monitoring programs, and the potential value of adjunctive medications with protective metabolic effects.

Keywords: Antipsychotics; Cardiovascular risk; Schizophrenia; Metabolic syndrome; IAS-AGLA score

1. Introduction

Schizophrenia is a severe and chronic psychiatric disorder characterized by disturbances in thought, perception, and behavior. Beyond its psychiatric manifestations, it exerts a profound impact on physical health, most notably cardiovascular disease (CVD), which is the leading cause of premature mortality in this population [1]. Patients with schizophrenia experience a reduction in life expectancy of 15–20 years compared to the general population, and epidemiological evidence consistently attributes the majority of this gap to cardiovascular causes [2].

The global prevalence of schizophrenia is approximately 1%, but its disproportionate burden is highlighted by disability-adjusted life years (DALYs) and excess mortality associated with the disorder [3]. The intersection of psychiatric illness and cardiovascular pathology reflects a convergence of biological, behavioral, and social determinants of health. Antipsychotic therapy, while indispensable for symptom control, contributes significantly to metabolic derangements. Second-generation antipsychotics (SGAs), such as clozapine and olanzapine, are particularly implicated in weight gain, insulin resistance, and dyslipidemia, although even metabolically safer agents, such as aripiprazole and ziprasidone, may indirectly contribute to cardiovascular burden [4,5].

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Beyond pharmacological effects, schizophrenia itself is associated with chronic low-grade inflammation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, and oxidative stress, all of which accelerate atherosclerosis [6]. Elevated circulating cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been identified in patients early in the disease course, even prior to pharmacological treatment [7]. Lifestyle factors further compound risk: individuals with schizophrenia are more likely to smoke, adopt sedentary behaviors, and follow poor dietary patterns [8]. In addition, structural barriers to care, including stigma and fragmented healthcare delivery, result in underdiagnosis and undertreatment of modifiable cardiovascular risk factors [9].

Epidemiological studies demonstrate the extent of the problem. A meta-analysis involving more than three million patients reported a twofold increase in cardiovascular mortality among individuals with schizophrenia and other severe mental illnesses [10]. These findings were consistent across diverse healthcare systems, suggesting that both biological predispositions and systemic treatment inequities contribute to elevated mortality. Importantly, access to preventive care is often inadequate: patients with schizophrenia are less likely to receive lipid-lowering therapies or antihypertensive medications despite meeting eligibility criteria [11]

In light of these concerns, comprehensive monitoring of cardiovascular health in patients treated with antipsychotics is critical. Preventive strategies must incorporate routine metabolic screening, early initiation of pharmacological interventions, and targeted lifestyle modifications. Furthermore, adjunctive pharmacological strategies, such as the use of GABAergic agents, may offer protective effects. Experimental evidence suggests that GABA signaling plays a role in modulating glucose metabolism, reducing systemic inflammation, and supporting endothelial function [12]. Preliminary clinical observations indicate potential cardioprotective benefits of drugs such as valproate, escitalopram, topiramate, and diazepam. However, systematic evaluation in real-world populations remains limited.

This study aimed to quantify cardiovascular risk in patients receiving long-term antipsychotic therapy, evaluate the prevalence of metabolic abnormalities, and assess whether adjunctive GABAergic medications may confer protective benefits. The findings provide insight into the urgent need for integrated care approaches to address both psychiatric and physical health outcomes in this vulnerable population.

2. Materials and Methods

This cross-sectional observational study was carried out at a tertiary psychiatric hospital. A total of 75 patients were recruited consecutively from outpatient clinics over a 12-month period. Inclusion criteria were: (i) confirmed diagnosis of schizophrenia or schizoaffective disorder according to DSM-5 criteria; (ii) continuous treatment with antipsychotic medication for at least five years; (iii) age between 18 and 70 years; and (iv) informed consent to participate. Exclusion criteria included acute systemic illness, recent hospitalization, non-adherence to antipsychotic therapy, or pregnancy/breastfeeding.

Demographic and clinical data were collected, including age, sex, smoking status, weight, height, body mass index (BMI), and waist circumference. Blood pressure was measured using validated devices under standardized conditions. Laboratory tests were performed after overnight fasting and included fasting glucose, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and C-reactive protein. Samples were processed in the hospital's accredited central laboratory.

Cardiovascular risk was estimated using the IAS-AGLA risk score, which incorporates age, sex, lipid profile, blood pressure, and smoking status. Patients were stratified into risk categories: low (<10%), moderate (10–15%), high (15–20%), and very high (>20%) 10-year CV risk. Therapeutic thresholds were based on LDL values adjusted for risk level: >189 mg/dL for low risk, >132 mg/dL for moderate risk, and >100 mg/dL for high/very high risk. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current antihypertensive therapy.

Pharmacological treatment data were carefully documented, with particular attention to adjunctive GABAergic drugs, including valproate, escitalopram, diazepam, and topiramate. The potential association between GABAergic therapy and cardiovascular risk was examined.

Statistical analysis included descriptive statistics (mean ± standard deviation for continuous variables, proportions for categorical variables). Group comparisons were performed using Student's t-test or ANOVA for continuous data, and chi-square tests for categorical variables. Logistic regression was applied to evaluate the independent association between GABAergic medication use and elevated CV risk, adjusting for age, sex, and BMI. Statistical significance was defined as $p<0.05$. Analyses were performed with SPSS version 25.0.

The study protocol was approved by the hospital's ethics committee, and all patients provided written informed consent. Patient confidentiality was maintained throughout the study.

3. Results

Seventy-five patients were included in the study, with a mean age of 47 ± 15 years. Forty-seven percent were female. The mean BMI was 30.9 ± 5.9 kg/m^2, and 48% of participants were classified as obese. Waist circumference exceeded recommended cutoffs in 45% of patients. Smoking prevalence was 52%.

Laboratory findings revealed a mean total cholesterol of 195.5 ± 40 mg/dL, LDL cholesterol 118.4 ± 33.8 mg/dL, HDL cholesterol 49.0 ± 17.2 mg/dL, and triglycerides 151.7 ± 75.4 mg/dL. Mean fasting glucose was 106.0 ± 29.8 mg/dL, with 22% of patients classified as prediabetic and 12% as diabetic. Mean HbA1c was 5.9 ± 0.9%. Elevated C-reactive protein levels (>3 mg/L) were identified in 28% of the cohort, consistent with systemic low-grade inflammation. Blood pressure measurements averaged 124 ± 16 mmHg systolic and 80 ± 10 mmHg diastolic. Hypertension was documented in 20% of patients.

According to IAS-AGLA stratification, 28% of patients were classified as having >10% 10-year cardiovascular risk. Among these, 16% met LDL thresholds for statin therapy, and 14.5% met criteria for antihypertensive treatment. Despite this, only 9% of patients were prescribed statins, and 11% were receiving antihypertensives, highlighting marked undertreatment of cardiovascular risk factors.

Sex-specific differences were observed. Men demonstrated higher LDL cholesterol levels (121.5 mg/dL vs. 114.2 mg/dL), whereas women exhibited higher triglyceride levels (158.2 mg/dL vs. 145.0 mg/dL). Patients older than 50 years were significantly more likely to fall into moderate or high CV risk categories ($p<0.05$).

Analysis by treatment regimen revealed that patients on clozapine or olanzapine had the most unfavorable metabolic profiles, with mean LDL levels exceeding 130 mg/dL and triglycerides above 170 mg/dL. By contrast, patients on aripiprazole or ziprasidone had more favorable lipid and glucose profiles. Those treated with risperidone and quetiapine fell in the intermediate range. These findings align with established metabolic risk hierarchies among antipsychotics.

Patients receiving GABAergic agents (n=18) demonstrated a significantly reduced probability of elevated cardiovascular risk. Logistic regression analysis confirmed that GABAergic drug use was independently associated with lower odds of elevated IAS-AGLA risk scores (OR=17, $p=0.049$), even after adjustment for confounders. This suggests a potential cardioprotective role, warranting further investigation.

Overall, the results underscore the clustering of metabolic risk factors among patients with schizophrenia under chronic antipsychotic therapy and highlight significant gaps in the management of these risks.

4. Discussion

This study provides important insights into the cardiovascular health of patients with schizophrenia and schizoaffective disorder undergoing long-term antipsychotic therapy. Nearly one-third of the cohort demonstrated elevated 10-year cardiovascular risk, consistent with international literature that documents a two- to threefold increase in cardiovascular mortality among patients with severe mental illness [10,11].

The association between SGAs, particularly clozapine and olanzapine, and adverse metabolic effects is well established [7]. These agents promote weight gain and metabolic dysregulation through antagonism of serotonin 5-HT2C and histamine H1 receptors, leading to hyperphagia and impaired energy homeostasis. Our results confirmed poorer lipid and glucose profiles among patients receiving these medications. Conversely, patients on aripiprazole and ziprasidone displayed more favorable parameters, highlighting the need to consider metabolic risk in treatment decisions [8].

Undertreatment of dyslipidemia and hypertension was a striking finding. Despite 16% of patients meeting criteria for lipid-lowering therapy and 14.5% for antihypertensives, actual prescription rates were below 10%. This discrepancy reflects systemic barriers, including fragmented care, lack of coordination between psychiatric and primary care services, and potential diagnostic overshadowing, where somatic symptoms are underestimated in psychiatric populations [12]. Addressing these gaps is essential to reducing excess cardiovascular mortality.

A novel and intriguing finding was the apparent protective association of GABAergic agents with cardiovascular risk. Experimental data indicate that GABA signaling exerts anti-inflammatory effects, enhances endothelial function, and regulates glucose metabolism [13,14]. Clinical evidence remains limited, but our results suggest that adjunctive use of GABAergic drugs such as valproate, diazepam, or escitalopram may mitigate antipsychotic-induced metabolic burden. Further prospective and interventional studies are needed to validate this observation and explore underlying mechanisms.

Comparison with international studies reveals similar trends. The prevalence of obesity, prediabetes, and dyslipidemia in our cohort aligns with estimates of 30–40% metabolic syndrome prevalence among patients with schizophrenia worldwide [8,17]. Systematic reviews confirm that cardiovascular mortality in this population remains disproportionately high despite advances in psychiatric treatment. Our findings reinforce the urgent need for integrated, multidisciplinary care models.

Clinical implications are clear. Routine cardiovascular risk assessment must become standard practice in psychiatric settings. This should include annual lipid panels, glucose monitoring, and blood pressure checks. Lifestyle interventions, while challenging in this population, are crucial. Tailored programs focusing on nutrition, physical activity, and smoking cessation may yield significant benefits. In addition, healthcare systems must ensure equitable access to preventive therapies, including statins and antihypertensives.

Limitations of this study include its cross-sectional design, modest sample size, and single-center setting, which limit generalizability and preclude causal inference. We did not assess dietary intake, physical activity, or genetic predispositions, which may influence metabolic outcomes. Nevertheless, the alignment of our findings with existing literature strengthens their relevance.

Future directions should focus on longitudinal studies to evaluate the trajectory of cardiovascular risk over time in patients on chronic antipsychotic therapy. Randomized controlled trials are needed to test the efficacy of integrated care models and the potential cardioprotective effects of GABAergic drugs. Policy-level initiatives aimed at reducing disparities in preventive care access will also be critical in addressing the mortality gap in this population.

5. Conclusion

In conclusion, this study demonstrates that patients with schizophrenia and schizoaffective disorder treated with long-term antipsychotics carry a substantial cardiovascular risk burden. Nearly one-third of patients exhibited elevated 10-year CV risk, with many meeting criteria for lipid-lowering or antihypertensive therapy. However, undertreatment was pervasive, emphasizing the urgent need for better integration of cardiovascular prevention into psychiatric care.

Our findings support routine metabolic screening, proactive management of dyslipidemia and hypertension, and adoption of lifestyle interventions tailored to psychiatric populations. The protective association of GABAergic agents, although preliminary, opens new avenues for research into adjunctive strategies aimed at mitigating cardiometabolic burden. Closing the mortality gap for patients with schizophrenia requires coordinated efforts at clinical, research, and policy levels, ensuring that psychiatric stability is achieved without compromising somatic health.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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