Research Article

Comparative Assessment of the Metabolic Impact of Risperidone and Trifluoperazine in Drug-Naïve Psychotic Patients: A Prospective Observational Study

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Background: Patients with schizophrenia face a 20% lower life expectancy than the general population, primarily due to cardiovascular complications linked to antipsychotic-induced metabolic syndrome.

Materials and Methods: This prospective, observational, non-randomised study compared the metabolic effects of risperidone (n=38) and trifluoperazine (n=38) in 76 drug-naïve patients over 12 weeks. Parameters included BMI, waist circumference, blood pressure, HbA1c, and lipid profiles.

Results: Significant baseline imbalances were noted, with the risperidone group exhibiting higher weight ($p = 0.002$) and BMI ($p = 0.002$). Post-treatment, risperidone induced a markedly higher metabolic burden, particularly in HbA1c (22.82% increase) and triglycerides (32.79% increase) compared to trifluoperazine.

Conclusion: Second-generation antipsychotics like risperidone carry a significantly higher metabolic liability than first-generation agents, necessitating early and vigilant metabolic monitoring.

Access this article online

Website: www.cijmr.com

DOI: 10.58999/cijmr.v5i02.370

Keywords: Schizophrenia, Risperidone, Trifluoperazine, Antipsychotics, Metabolic changes

Introduction

Psychotic disorders, particularly schizophrenia, are among the most disabling and chronic mental health conditions, affecting individuals worldwide.[1] These disorders not only cause profound psychological and social impairments but also significantly increase the physical health burden on affected individuals. Among people with schizophrenia, the average life expectancy is 20% lower than that of the general population.[2] Cardiovascular complications, often stemming from metabolic disturbances induced by antipsychotic medications, account for the majority of these premature deaths rather than suicide, which is more commonly associated with these disorders.[3] This highlights the importance of addressing the broader physiological effects of psychotropic medications to improve the overall health and longevity of patients.

The prevalence of metabolic disturbances among patients with psychotic disorders varies widely, ranging from 3.3 to 68.6%, depending on factors such as age, sex, ethnicity, and lifestyle.[4] Patients with psychosis are often at a higher risk of developing metabolic syndrome compared to the general population due to a combination of medication effects, unhealthy lifestyle choices, and pre-existing vulnerabilities. Unhealthy dietary patterns, sedentary behavior, substance use (including tobacco and alcohol), and inadequate access to healthcare further compound this risk. Moreover, conditions such as hepatobiliary disease, polycystic ovary syndrome, and mood disorders, along with genetic predisposition and disrupted sleep patterns, exacerbate metabolic dysfunction in this population.[5] Most existing literature focuses on these drug classes independently or in patients with prior medication history, which can obscure the unmodified effects of the drugs. Furthermore, South Asian populations possess a unique genetic and dietary predisposition to central obesity and insulin resistance, making region-specific data a clinical necessity.

This study sought to address these deficiencies by evaluating and comparing the frequency and magnitude of metabolic changes induced by risperidone and trifluoperazine in a drug-naïve cohort over a three-month follow-up period.

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Submitted: 04/04/2026 Revision: 04/04/2026

Accepted: 02/05/2026 Published: 15/08/2026

How to cite this article: Rathore S, Motiyani A, Sharma D. Comparative Assessment of the Metabolic Impact of Risperidone and Trifluoperazine in Drug-Naïve Psychotic Patients: A Prospective Observational Study. Central India Journal of Medical Research. 2026;5(2):68-73.

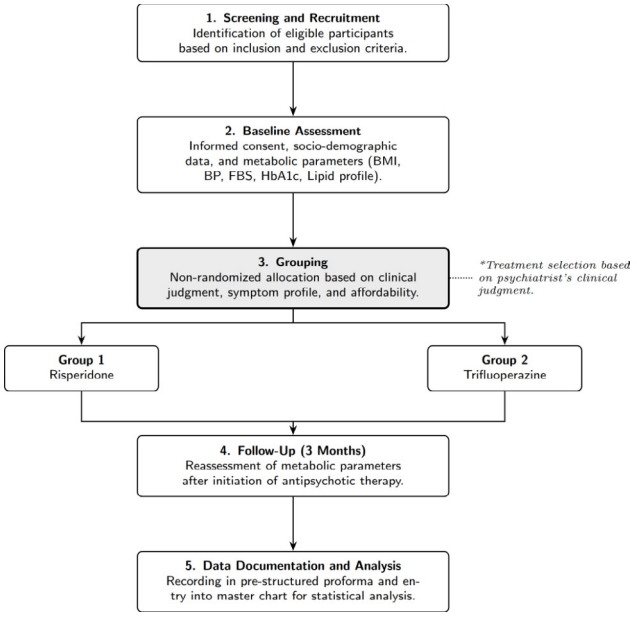

Figure 1: Study procedure

Methodology

It is a prospective, observational, non-randomized comparative study conducted to assess and compare the metabolic effects of risperidone and trifluoperazine among drug-naïve psychotic patients with schizophrenia or other psychotic disorders according to the International Classification of Diseases-10 (ICD-10) criteria attending the Psychiatry OPD of a tertiary care hospital. The study included 76 participants, with 38 patients in each group (Risperidone and Trifluoperazine groups). Participants were selected through purposive sampling from eligible patients attending the Psychiatry OPD. The study was initiated after obtaining approval from the Institutional Ethics Committee of the Medical College. Written informed consent was obtained from all participants, and confidentiality of their medical and personal information was maintained. Eligible patients were aged 18 to 45 years, diagnosed with psychotic disorders per ICD-10 criteria, and were strictly drug-naïve with no prior antipsychotic exposure. Exclusion criteria included patients unable to cooperate due to severe psychosis; a history of psychotropic use; or pre-existing comorbidities such as diabetes mellitus, systemic hypertension, dyslipidemia, thyroid disease, epilepsy, or head injury, which could independently alter metabolic markers. Participants were assured of their right to withdraw from the study at any time without any impact on their ongoing treatment. To ensure comprehensive and standardized data collection, a semi-structured proforma was used to collect detailed information on demography, clinical profile, family history, anthropometric and physical measurements were measured, laboratory investigations were done. International Classification of Diseases, 10th Revision (ICD-10), MSE were used as a diagnostic tool. Procedure (Figure 1).

Table 1: Distribution of baseline clinical and biochemical parameters

Parameter	*Mean ± SD*	*Minimum*	*Maximum*
Height (m)	1.61 ± 0.12	1.3	1.89
Weight (kg)	57.70 ± 13.82	40.55	105.2
BMI	22.74 ± 7.21	11.35	46.87
Waist circumference (cm)	82.48 ± 15.19	60.06	123.06
Systolic BP (mmHg)	124.86 ± 6.67	110.0	130.0
Diastolic BP (mmHg)	79.63 ± 5.08	70.0	84.0
Fasting blood sugar (mg/dl)	90.95 ± 10.47	71.53	119.0
HbA1c (%)	5.25 ± 0.44	4.51	6.8
Total cholesterol (mg/dl)	174.35 ± 28.00	130.73	278.77
LDL (mg/dl)	112.37 ± 16.15	61.14	179.29
HDL (mg/dl)	46.07 ± 6.98	30.58	59.94
Triglycerides (mg/dl)	101.70 ± 32.10	11.44	151.77

Table 2 : Clinical and biochemical parameters at 3 months

Parameter	*Mean ± SD*	*Maximum*	*Minimum*
Weight (kg)	59.3443 ± 14.0058	107.43	41.83
BMI	23.3911 ± 7.3324	48.1	11.71
Waist circumference (cm)	83.023 ± 15.2922	124.06	60.77
Systolic BP (mmHg)	134.026 ± 6.5442	142.0	118.0
Diastolic BP (mmHg)	88.605 ± 6.3163	96.0	70.0
Fasting blood sugar (mg/dl)	95.0934 ± 10.3649	123.0	77.0
Total cholesterol (mg/dl)	184.515 ± 31.9414	300.46	133.0
LDL (mg/dl)	117.6934 ± 21.7892	188.29	11.89
HDL (mg/dl)	44.6017 ± 7.3284	58.58	27.86
Triglycerides (mg/dl)	119.4213 ± 30.8649	202.72	39.48

Table 3: Comparative analysis of metabolic parameters between risperidone and trifluoperazine at baseline and after 3 months

Parameter	*Risperidone at baseline*	*Risperidone at 3 months*	*Trifluoperazine at baseline*	*Trifluoperazine at 3 months*	*p-value**
Weight (kg)	62.58	64.70	52.83	53.98	0.001
BMI	25.28	26.13	20.21	20.64	0.001
Waist Circumference (cm)	86.56	87.41	78.39	78.62	0.011
Systolic BP (mmhg)	123.94	134.68	125.78	133.36	0.384
Diastolic BP (mmhg)	79.63	90.36	79.63	86.84	0.014
FBS (mg/dl)	91.29	97.45	90.61	92.73	0.047
Hba1c	5.33	6.55	5.17	5.35	<0.001
Total cholesterol (mg/dl)	177.57	192.87	171.13	176.15	0.022
LDL (mg/dl)	113.87	124.97	110.87	110.41	0.003
HDL (mg/dl)	42.14	40.16	50.01	49.03	<0.001
Triglycerides (mg/dl)	90.17	119.74	113.23	119.1	0.928

Sample size

The required sample size was calculated as 76 participants, with 38 patients in each group (Risperidone and Trifluoperazine groups). This calculation was based on the hypothesis of a 40% difference in metabolic syndrome prevalence between the groups: 20% Metabolic syndrome in the trifluoperazine group and 60% metabolic syndrome in risperidone group, using an 80% power and a 1% significance level, with a 10% allowance for dropout.

Statistical Analysis

The collected data were analyzed using SPSS software (version 29.0). Numerical data were expressed as mean, standard deviation, and range, while categorical data were presented as frequencies and percentages. An appropriate statistical test was applied. A *p-value* of less than 0.05 was considered statistically significant.

Table 4: Comparative analysis of metabolic parameters between risperidone and trifluoperazine

Parameter	*%Change (Risperidone)*	*%Change (Trifluoperazine)*
Weight (kg)	3.4	2.18
BMI	3.36	2.16
Waist circumference (cm)	0.98	0.29
Systolic BP (mmHg)	8.66	6.02
Diastolic BP (mmHg)	13.48	9.05
FBS (mg/dl)	6.75	2.34
HbA1c	22.82	3.55
Total cholesterol (mg/dl)	8.62	2.94
LDL (mg/dl)	9.75	-0.42
HDL (mg/dl)	-4.69	-1.95
Triglycerides (mg/dl)	32.79	5.18

Ethical Considerations

The study was initiated after obtaining approval from the Institutional Ethics Committee of the Medical College (letter no IEC-RDGMC-PG/PSYCHIATRY/72 dated 02/08/2023). Written informed consent was obtained from all participants, and confidentiality of their medical and personal information was maintained. Participants were assured of their right to withdraw from the study at any time without any impact on their ongoing treatment.

Result

Demography

The participants had an average age of 34.55 years (SD = 8.28), with ages ranging from 19 to 45 years. Of the total, 59.2% (n = 45) were male and 40.8% (n = 31) were female. In terms of education, the largest proportion had completed middle school (27.6%), followed by high school graduates (26.3%) and those who were illiterate (22.4%). Occupationally, semi-skilled workers formed the largest group (25.0%), while 23.7% were unemployed and 19.7% were skilled workers. Regarding income, most participants reported earning between ₹1,000 and ₹5,000 per month (23.7%), whereas only a small fraction (5.3%) earned between ₹50,000 and ₹1,00,000. Socioeconomic classification revealed that 65.8% belonged to the upper-lower class and 34.2% to the lower-middle class. Marital status distribution showed that 39.5% were unmarried, 28.9% married, 15.8% separated, and 7.9% each were widowed or widowers.

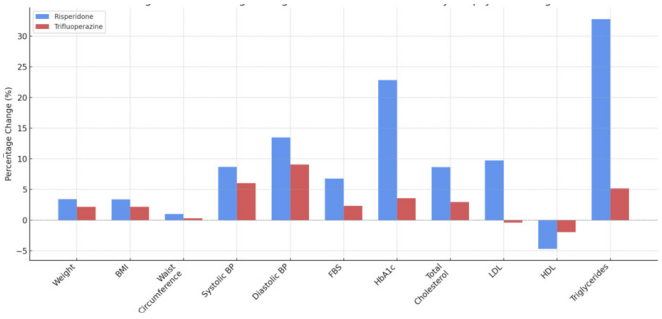

Figure 2: Comparative analysis of metabolic parameters between risperidone and trifluoperazine

Clinical profile

About 57.9% of participants had a family history of psychiatric illness. Common substances used in substance use patterns were found to be tobacco (26.3%) and alcohol (17.1%).

Clinical and Biochemical Parameters

Table 1 depicts baseline clinical and biochemical parameters. Notably, a baseline imbalance existed between the groups; participants assigned to risperidone were significantly older and had a higher baseline weight, BMI, and waist circumference compared to the trifluoperazine group (Tables 2-4 and Figure 2).

Discussion

The present study was undertaken with the primary aim of assessing and comparing the metabolic parameters among patients with schizophrenia receiving risperidone and trifluoperazine. The specific objectives included the evaluation of anthropometric parameters (weight, body mass index, waist circumference), blood pressure, and metabolic indices (fasting blood glucose, HbA1c, lipid profile) at baseline and after a 3-month follow-up period.

Socio-demographic Characteristics and Their Relationship with Psychotic Disorders

The socio-demographic findings from our study align closely with previously published literature regarding the typical profile of psychotic patients. Patel *et al*.[6] and Subramaniam *et al*.[7] have reported that psychotic disorders, particularly schizophrenia, predominantly affect young adults, typically in the age group of 20 to 40 years. This trend is consistent with our finding of a mean participant age of approximately 34 years. Additionally, similar demographic patterns regarding gender distribution have been documented by Hegde *et al*.,[8] who noted a higher prevalence among males. This gender disparity is also evident in our data, where male participants (59.2%) significantly outnumbered female participants. Socioeconomic adversity is frequently linked with psychotic disorders, as emphasized by Wainberg *et al*.[9] Economic disadvantages compound the disease burden by affecting patients' access to timely treatment, medication adherence, and consistent follow-up care. Moreover, lower educational attainment, a notable finding in our study (27.6% middle school, 22.4% illiterate), further complicates treatment compliance and effective communication of medical advice, aligning with Nazir *et al*.,[10] who reported similar educational vulnerabilities among psychotic populations in India.

Role of Substance Use and Family Psychiatric History as Risk Factors

Substance use was present in 45 participants (59.2%), with tobacco being the most frequently used substance (26.3%), followed by alcohol (17.1%) and other substances (15.8%). A positive family history of psychiatric disorders was reported in 44 participants (57.9%). According to Cather *et al*.,[11] smoking is disproportionately prevalent among individuals with schizophrenia and significantly contributes to insulin resistance, dyslipidemia, and cardiovascular risk, thus compounding the metabolic burden imposed by antipsychotic treatment. Williams and Periasamy,[12] who highlighted the contribution of genetic and environmental factors to visceral adiposity and metabolic risk, especially in Asian populations. A family history of psychiatric illness can signal a greater genetic vulnerability not just for psychotic disorders but also for treatment-related metabolic complications due to inherited metabolic profiles and lifestyle patterns shared within families.

Metabolic Effects: Comparison of Risperidone and Trifluoperazine

In this study, both the risperidone and trifluoperazine groups exhibited significant increases in body weight and BMI over three months of treatment. However, the Risperidone group showed a markedly more pronounced effect. The mean weight in the risperidone group increased from 62.58 kg at baseline to 64.70 kg after three months, whereas the trifluoperazine group saw a more modest increase from 52.83 to 53.98 kg. Similarly, BMI rose from 25.28 to 26.13 in the risperidone group, compared to 20.21 to 20.65 in the trifluoperazine group. In this study, patients treated with risperidone exhibited comparatively higher baseline values for weight, BMI, waist circumference, and lipid parameters than those receiving trifluoperazine. These pre-existing differences may have predisposed to more rapid

metabolic decline when exposed to SGAs. Accordingly, the more pronounced metabolic alterations observed in the Risperidone group may not be entirely attributable to the pharmacological effect of the drug but could partly reflect underlying baseline metabolic vulnerability.

Dietary habits were another important confounding factor that could not be completely controlled during the study. Variations in calorie intake, nutritional status, consumption of high-fat or high-carbohydrate diets, eating behavior, and irregular meal patterns may have contributed to changes in body weight, blood glucose, and lipid profile. Patients with psychotic disorders often have unhealthy dietary practices and sedentary lifestyles, which independently predispose them to metabolic abnormalities. Similarly, physical activity levels, smoking, alcohol use, socioeconomic conditions, and family support systems may also have acted as confounding variables influencing metabolic outcomes.

This trend aligns with the findings of Pérez-Iglesias *et al*.,[13] who reported an average weight gain of 5.6 kg in drug-naïve patients treated with risperidone over 12 weeks. Our study showed a significant increase in waist circumference in both groups, but the change was more substantial in the risperidone group (from 86.57–87.42 cm) compared to the trifluoperazine group (from 78.39–78.63 cm). De Hert *et al*.[14] and Mitchell *et al*.[15] emphasized that increased waist circumference is a hallmark of metabolic syndrome in schizophrenia patients on antipsychotic therapy, particularly with SGAs. Both treatment arms demonstrated a statistically significant rise in systolic and diastolic blood pressure after three months. De Hert *et al*.[14] reported hypertension as one of the common metabolic abnormalities associated with SGAs.

Glycemic Control in Drug-Naïve Patients

The present study observed a statistically significant increase in glycemic indices—fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) after three months of antipsychotic treatment. The mean HbA1c in the risperidone group statistically increased from 5.34 to 6.55%, while in the trifluoperazine group, it rose from 5.17 to 5.36%. Makary *et al*.[16] reported a significant rise in HbA1c among children and adolescents treated with SGAs, reinforcing the early and robust impact of these drugs on glucose metabolism.

Lipid profile

The study demonstrated a statistically significant alteration in lipid parameters after three months of antipsychotic therapy, with more pronounced dyslipidemia observed in patients treated with risperidone compared to those on trifluoperazine. De Hert *et al*.[14] extensively reviewed the relationship between antipsychotic use and metabolic syndrome, concluding that SGAs, particularly risperidone, are associated with increased triglycerides, elevated total and LDL cholesterol, and reduced HDL levels. The results of this study highlight the importance of routine lipid monitoring in patients prescribed SGAs, particularly risperidone. Dyslipidemia, as evidenced by elevated LDL and total cholesterol and reduced HDL, is a major modifiable risk factor for cardiovascular morbidity and mortality. The metabolic changes observed within a relatively short period (12 weeks) suggest that these adverse effects may emerge early during treatment and necessitate prompt detection. Clinical protocols should include baseline lipid profiling prior to initiating antipsychotic treatment, followed by periodic assessments throughout therapy.

Strengths

Drug-Naïve Cohort: By involving only drug-naïve patients, the study successfully eliminated the confounding influence of prior antipsychotic exposure, providing a "clean slate" for metabolic assessment.

Comprehensive Assessment

The inclusion of both anthropometric (waist circumference, BMI) and biochemical (HbA1c, full lipid profile) markers provided a holistic view of the patients' cardiometabolic risk.

Limitations

Despite its clinical relevance, several limitations must be acknowledged. The significant pre-existing differences in weight, BMI, and age between the two groups introduce a high risk of confounding, as the risperidone group was metabolically "heavier" at the outset. The use of purposive sampling rather than random assignment introduces potential selection bias, lack of blinding for both investigators and participants may have influenced the reporting of lifestyle habits or the management of side effects. Also follow up duration might be small for adequate assessment of metabolic syndrome.

Small Sample Size

While the sample size of 76 was justified by a hypothesis-testing calculation (aiming for 80% power and 1% significance), it remains relatively small for detecting subtle differences in secondary outcomes or performing complex subgroup analyses.

Conclusion

This study demonstrates that antipsychotic medications, particularly second-generation agents like risperidone, are significantly associated with adverse metabolic changes in drug-naïve patients with schizophrenia. Over a three-month period, patients receiving risperidone showed a greater increase in weight, body mass index, waist circumference, fasting blood sugar, HbA1c, total cholesterol, LDL, and triglyceride levels, along with a more pronounced reduction in HDL cholesterol compared to those treated with trifluoperazine. Although both drugs were effective in the psychiatric management of schizophrenia, risperidone was found to have a significantly higher metabolic burden. These findings emphasize the importance of integrating routine metabolic monitoring and individualized risk assessment into psychiatric practice, particularly when initiating treatment with atypical antipsychotics.

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