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Research Article

Comparative Evaluation of Metabolic Adverse Effects of Olanzapine and Risperidone in Patients with Schizophrenia: A Prospective Study

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ABSTRACT

Background: People with schizophrenia carry a raised cardiometabolic risk, and antipsychotic treatment can add to it. Knowing how commonly prescribed agents compare helps clinicians in Pakistan choose and monitor treatment.

Objective: To compare the metabolic adverse effects of olanzapine and risperidone in patients with schizophrenia attending tertiary hospitals in Pakistan.

Methods: This multicenter prospective observational study enrolled 140 adults starting olanzapine or risperidone monotherapy (70 per group), recruited during 2025 and followed for 24 weeks. Anthropometric and biochemical changes were compared with baseline-adjusted models using robust standard errors.

Results: Follow-up was completed by 132 participants (66 per group). Weight rose by 5.60 ± 2.24 kg with olanzapine and 2.31 ± 2.63 kg with risperidone, an adjusted difference of 3.60 kg (95% confidence interval 2.74–4.46; p<0.001). Weight gain of at least 7% occurred in 69.7% and 24.2% of patients, respectively. Olanzapine was associated with further increases in fasting glucose (8.46 mg/dL) and HbA1c (0.20 percentage points), larger rises in triglycerides and waist circumference, and a greater fall in HDL cholesterol. Metabolic syndrome developed in 40.9% versus 10.6%. Sensitivity analyses supported the weight result.

Conclusion: Risperidone showed a clearly more favorable metabolic profile than olanzapine over 24 weeks. Simple routine checks of weight, waist, glucose, and lipids allow early detection and timely action with either drug.

Keywords: Schizophrenia, olanzapine, risperidone, metabolic syndrome.

INTRODUCTION

Schizophrenia shortens life, and much of the excess mortality comes from physical illness rather than psychosis itself. A large meta-analysis found raised mortality from several natural causes, including cardiovascular disease and diabetes.[1] Even so, long-term cohort data link antipsychotic use with lower mortality than nonuse,[2] so the task is to keep patients on effective treatment while managing its physical cost. Choosing an antipsychotic means weighing symptom control, tolerability, previous response, and patient preference. The American Psychiatric Association guideline recommends monitoring both benefit and adverse effects throughout treatment.[3] Network meta-analysis of maintenance treatment also shows that tolerability matters when choosing among effective drugs, particularly when treatment will continue for years.[4]

Individual antipsychotics differ markedly in their metabolic effects. In one network meta-analysis, olanzapine ranked among the worst drugs for weight and several biochemical measures, while risperidone fell in the middle.[5] These differences in weight, glucose, and lipids persist during longer treatment,[6] so the first prescribing decision has lasting consequences for physical health.

Dose complicates comparisons, because the relationship between dose and weight

gain differs across drugs and is not always linear.[7] Differences in histaminergic, serotonergic, and other receptor activity help explain why appetite, sedation, and metabolic tolerability vary between agents.[8] Second-generation antipsychotics should therefore be compared individually rather than treated as one metabolically uniform class.

Metabolic risk also depends on factors present before treatment, such as adiposity, lifestyle, and the illness itself, which interact with medication exposure.[9] Monitoring guidance therefore recommends a baseline assessment and repeat measurements after treatment starts, because clinically important changes can appear before patients notice them.[10] Waist circumference, measured with weight, gives a simple index of central adiposity at routine visits.

Because individual drugs do not affect weight, glycemia, blood pressure, and lipids in the same way, these outcomes are best assessed together.[11] In Pakistan, Hussain and colleagues compared the two drugs in newly diagnosed psychiatric patients at a single military institute and found differences in metabolic outcomes,[12] but multicenter data restricted to schizophrenia are still limited.

Local data matter. The GEN SCRIP study described poor physical health and a high prevalence of cardiovascular risk factors among people with schizophrenia in Pakistan.[13] A recent meta-analysis also showed that antipsychotics can disturb glucose regulation independently of their tendency to cause weight gain,[14] so biochemical testing cannot be replaced by weighing patients. The present study therefore compared 24-week changes in weight, glucose regulation, lipids, and metabolic syndrome in patients starting olanzapine or risperidone at tertiary hospitals, with emphasis on baseline-adjusted differences and clinically meaningful events.

MATERIALS AND METHODS

This prospective cohort study was conducted in three tertiary hospitals in Pakistan. Consecutive patients were recruited from 1 January to 31 December 2025 and followed for 24 weeks; follow-up ended on 30 June 2026. The treating psychiatrist chose olanzapine or risperidone as part of routine care, independently of study assessments, so allocation was not randomized. Seventy participants started each drug.

Adults aged 18–60 years with a DSM-5 diagnosis of schizophrenia were eligible if previous antipsychotic exposure did not exceed seven days. Exclusion criteria were established diabetes, metabolic syndrome at baseline, pregnancy or lactation, major endocrine disease, severe hepatic or renal impairment, systemic corticosteroid use, use of weight-reducing medicines, and need for antipsychotic combination therapy. Patients with isolated metabolic abnormalities were eligible if they did not meet metabolic syndrome criteria.

The sample size was based on detecting a 2.0-kg between-group difference in weight change, assuming a common standard deviation of 3.8 kg, two-sided alpha of 0.05, and 80% power. This required 57 participants per group, or 68 after allowing for 15% attrition; the target was rounded up to 70 per group (140 in total). These figures were planning assumptions, not estimates of the observed effect.

Olanzapine was given at 10–20 mg/day and risperidone at 2–6 mg/day, adjusted for symptoms and tolerability. Dose and adherence were recorded at each visit from patient interviews, prescription review, and, when appropriate, caregiver reports. Both groups received the same dietary and physical-activity advice. No participant switched drugs or received an additional antipsychotic before the last recorded assessment.

Baseline data included age, sex, illness duration, smoking, family history of diabetes, and Positive and Negative Syndrome Scale (PANSS) score. Weight was measured on calibrated scales in light clothing without shoes. Height was measured at enrollment, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured midway between the lowest rib and the iliac crest. Blood pressure was the mean of two seated readings taken after five minutes of rest.

Weight was recorded at baseline and at weeks 4, 8, 12, and 24. Waist circumference, blood pressure, fasting plasma glucose, HbA1c, and lipid profile were recorded at baseline and at weeks 12

and 24, with blood drawn after an overnight fast of at least eight hours. LDL cholesterol was calculated with the Friedewald equation; all triglyceride values were below 400 mg/dL. Outcome definitions are given in Table 1. Abnormal screening values were not treated as confirmed clinical diagnoses.

Table 1. Operational definitions of metabolic outcomes

Outcome	Definition
Primary outcome	Baseline-adjusted difference in weight change at week 24, in kilograms
Clinically significant weight gain	Increase of at least 7% from baseline weight
Central adiposity component	Waist ≥90 cm in men or ≥80 cm in women
Triglyceride component	Fasting triglycerides ≥150 mg/dL or relevant treatment
HDL component	HDL <40 mg/dL in men or <50 mg/dL in women, or relevant treatment
Blood pressure component	Systolic pressure ≥130 mmHg, diastolic pressure ≥85 mmHg, or antihypertensive treatment
Glucose component	Fasting plasma glucose ≥100 mg/dL or treatment for elevated glucose
Incident metabolic syndrome	At least three of the five components at week 24; absent at baseline

HDL, high-density lipoprotein. Ethnicity-specific waist thresholds were used. Incidence of each component excludes participants who had that abnormality at baseline.

Analyses were performed in Python 3.12 using NumPy, pandas, SciPy, and statsmodels. Continuous variables are summarized as mean ± standard deviation (SD) or median (interquartile range). Baseline balance was described with standardized mean differences (SMDs) rather than significance tests. For the primary outcome, week-24 weight was analyzed by analysis of covariance (ANCOVA) adjusted for baseline weight, age, sex, smoking, baseline PANSS score, and hospital, with HC3 robust standard errors and 95% confidence intervals (CIs). The adjusted treatment coefficient estimates the between-group difference in weight change.

Secondary continuous outcomes were analyzed in the same way. Triglycerides were log-transformed and the treatment effect back-transformed to a ratio of geometric means. Binary outcomes were compared with Fisher exact tests, risk ratios (RRs) with log-based CIs, and risk differences with Newcombe CIs. The primary analysis used complete week-24 data. Sensitivity analyses carried baseline weight forward for missing outcomes and applied a 2-kg differential shift to missing outcomes. Secondary comparisons were exploratory and not adjusted for multiplicity; significance for the primary outcome was set at two-sided $p<0.05$.

RESULTS

Of 168 patients screened, 140 were enrolled. Four patients in each group missed the week-24 visit, leaving 66 completers per group. All earlier assessments were complete, and nobody switched medication.

Baseline characteristics are shown in Table 2. The largest imbalance was in PANSS score, which was included as a covariate in all adjusted models.

Table 2. Baseline demographic and clinical characteristics

Characteristic	Olanzapine (n = 70)	Risperidone (n = 70)	SMD
Age, years	35.9 ± 9.6	35.0 ± 8.1	0.10
Male sex, n (%)	41 (58.6)	41 (58.6)	0.00
Illness duration, months	16.2 (13.0–19.7)	16.3 (10.9–19.0)	0.19
Current smoking, n (%)	14 (20.0)	15 (21.4)	-0.04
Family history of diabetes, n (%)	26 (37.1)	22 (31.4)	0.12
Weight, kg	64.9 ± 10.1	63.9 ± 11.5	0.09

Characteristic	Olanzapine (n = 70)	Risperidone (n = 70)	SMD
BMI, kg/m²	23.7 ± 2.7	23.7 ± 3.0	0.01
Waist circumference, cm	78.4 ± 8.4	77.8 ± 7.3	0.07
Fasting glucose, mg/dL	91.3 ± 8.3	90.2 ± 7.3	0.14
Triglycerides, mg/dL	118.6 ± 22.7	116.4 ± 21.8	0.10
PANSS total score	82.9 ± 12.1	88.1 ± 11.7	-0.44

Values are mean ± SD, median (IQR), or n (%). SMD, standardized mean difference (olanzapine minus risperidone); PANSS, Positive and Negative Syndrome Scale; BMI, body mass index.

Weight, BMI, and waist circumference rose more with olanzapine at every time point (Figure 1). Glycemic and lipid changes were also less favorable with olanzapine (Figure 2).

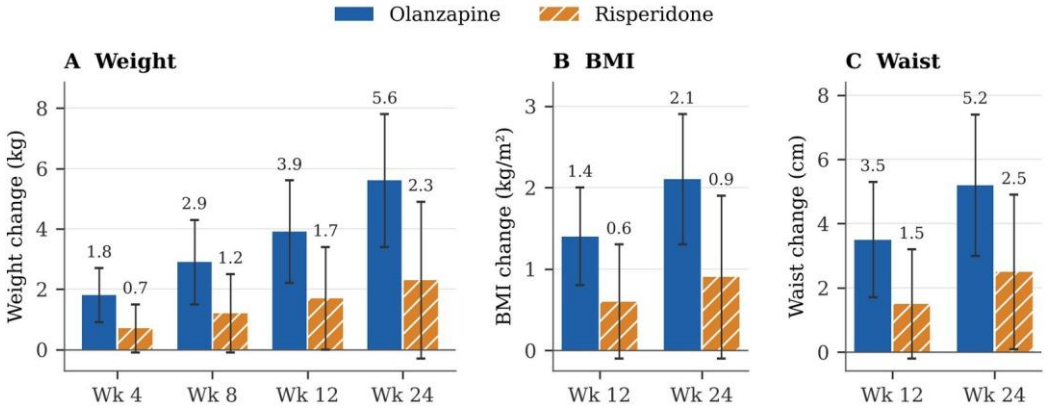

Figure 1. Anthropometric changes from baseline over 24 weeks

Bars show mean change; error bars show SD. Each group contributed 70 observations at weeks 4, 8, and 12, and 66 at week 24. BMI, body mass index.

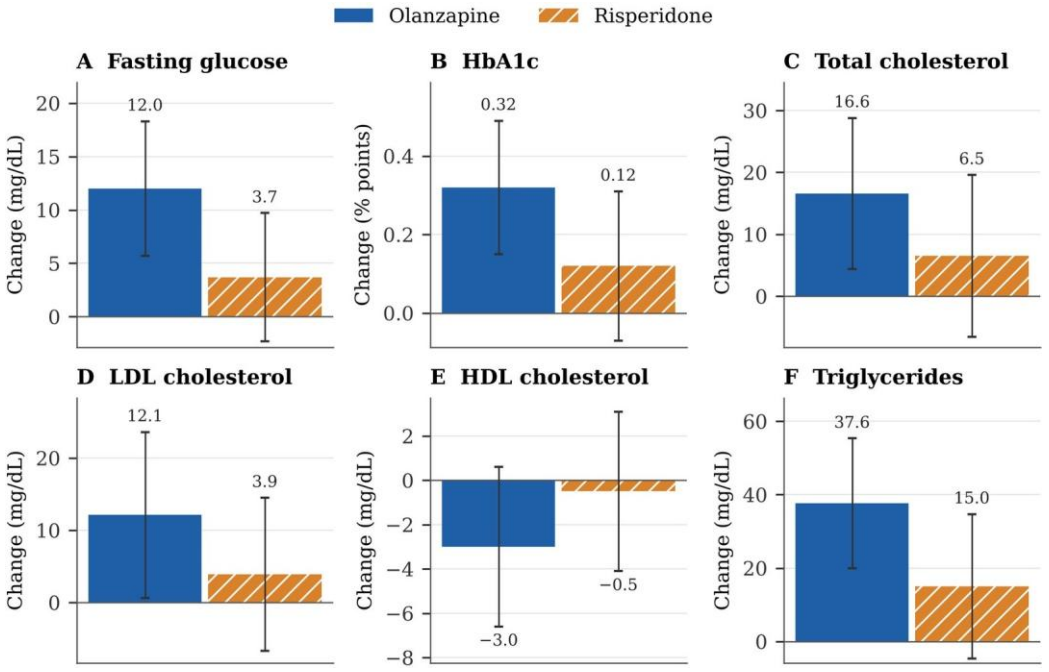

Figure 2. Biochemical changes from baseline to week 24

Bars show mean change; error bars show SD (n = 66 per group). HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Screening abnormalities were not equated with confirmed diabetes.

Incident metabolic events are shown in Figure 3. The risk difference for metabolic syndrome was 30.3 percentage points (95% CI 15.6–43.5), and the risk of at least 7% weight gain was almost three times higher with olanzapine (RR 2.88; 95% CI 1.82–4.53). These secondary comparisons are exploratory and unadjusted.

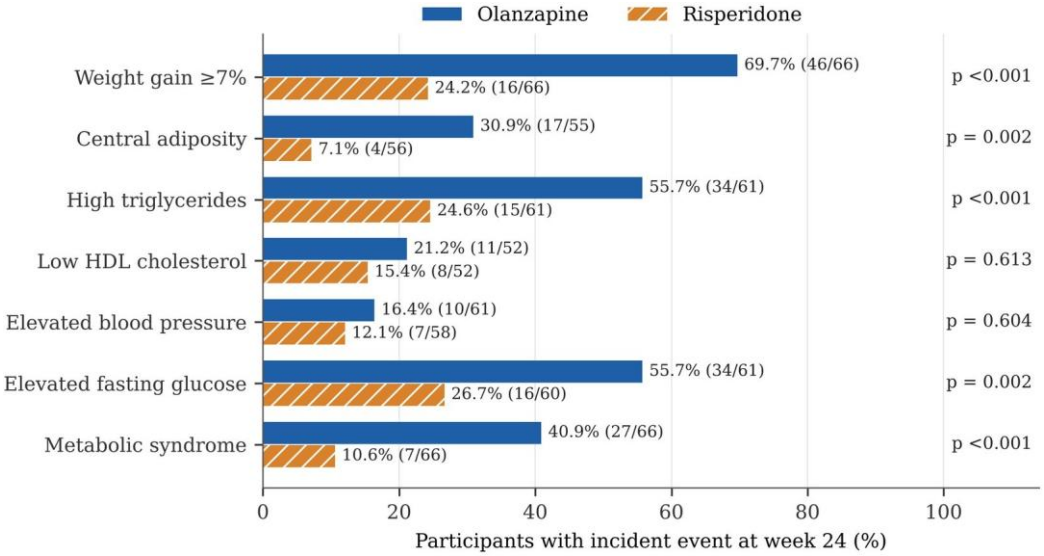

Figure 3. Incident metabolic events at week 24

Labels show percentage (n/N). N is the number of completers free of the relevant abnormality at baseline; all 132 completers were free of metabolic syndrome at baseline. p values are from exploratory two-sided Fisher exact tests.

Adjusted differences appear in Table 3. The adjusted weight difference (3.60 kg) was slightly larger than the raw one (3.29 kg), mainly because the olanzapine group started with lower PANSS scores. The result held when missing outcomes were replaced by baseline values (3.49 kg; 95% CI 2.64–4.34) and when a differential shift was applied to them (3.40 kg; 95% CI 2.57–4.23).

Table 3. Adjusted between-group comparisons at week 24

Outcome	Estimate (95% CI)	p value
Weight, kg	3.60 (2.74 to 4.46)	<0.001
Waist, cm	2.89 (2.04 to 3.75)	<0.001
Fasting glucose, mg/dL	8.46 (6.25 to 10.67)	<0.001
HbA1c, percentage points	0.20 (0.14 to 0.27)	<0.001
Total cholesterol, mg/dL	10.26 (5.77 to 14.75)	<0.001
LDL cholesterol, mg/dL	8.15 (4.15 to 12.16)	<0.001
HDL cholesterol, mg/dL	-2.58 (-4.00 to -1.17)	<0.001
Triglycerides, ratio	1.19 (1.13 to 1.25)	<0.001

ANCOVA adjusted for the baseline value of the outcome, age, sex, smoking, baseline PANSS, and hospital, with HC3 robust standard errors. Differences are olanzapine minus risperidone; triglycerides are expressed as a ratio of adjusted geometric means. Secondary p values are unadjusted and exploratory.

DISCUSSION

Patients starting olanzapine gained more weight and had worse glucose and lipid changes than those starting risperidone. The gap in weight was 3.60 kg after adjustment, and clinically significant weight gain was almost three times as common. Yang and Wu, comparing the same two drugs, found that metabolic abnormalities and weight change did not move in step,[15] which suggests that the glucose and lipid findings here add information beyond weight alone.

Because participants had little previous antipsychotic exposure, these results reflect early treatment. Li and colleagues reported increases in BMI and insulin resistance after four weeks of olanzapine in drug-naïve patients, without a parallel rise

in fasting glucose.[16] Longer observational follow-up has also linked olanzapine with worse adiposity and lipid outcomes than risperidone.[17] The present findings fit this broad pattern, although they cannot show that the mechanisms or effect sizes are the same.

The pattern of weight gain is also consistent with data from early illness. A meta-analysis found substantial olanzapine-associated weight gain, larger in studies lasting more than 13 weeks.[18] Risperidone is not free of risk: Gao and colleagues observed weight gain over 12 weeks in medication-naïve patients.[19] In this cohort, nearly one in four risperidone-treated patients gained at least 7% of body weight, so a favorable comparison with olanzapine is no reason to relax monitoring. Responding to metabolic deterioration means balancing physical risk against psychiatric stability. A meta-analysis of switching studies found improvement in some weight and metabolic outcomes after a change to a lower-risk drug, depending on the drug chosen.[20] Dose reduction, discontinuation, or switching, however, produced only modest average weight loss.[21] Established weight gain may not reverse easily, which argues for early detection and individualized decisions.

Metformin is another option. A GRADE-based guideline supports its use for antipsychotic-induced weight gain, with attention to tolerability, renal function, and patient preference.[22] A later meta-analysis found that starting metformin together with the antipsychotic reduced weight gain and several metabolic changes,[23] and prevention guidance now recommends this approach in selected cases, including treatment with high-risk drugs.[24] The present study did not evaluate preventive treatment, its cost, or its effectiveness in Pakistani services.

A recent randomized trial found that adjunctive semaglutide improved glucose control and weight in patients taking olanzapine or clozapine who had early glycemic abnormalities.[25] Cost and supply will shape how widely such options can be used locally, but regular weighing and basic blood tests are already available in every participating hospital.

The study has clear strengths. Recruitment spanned multiple hospitals, patients were almost drug-naive at entry, and follow-up was nearly complete, with 94% of participants reaching week 24. Measurements were standardized and repeated, so early trajectories were captured rather than inferred, and the main result held across sensitivity analyses. Two limitations should be kept in mind. Treatment was not randomized, so some residual confounding is possible despite adjustment. And because patients with diabetes or metabolic syndrome were excluded and follow-up lasted 24 weeks, the findings apply to early treatment in metabolically healthier patients rather than to long-term cardiovascular outcomes.

CONCLUSION

Risperidone carried a substantially lower metabolic burden than olanzapine during the first 24 weeks of treatment, with less weight gain, smaller changes in glucose and lipids, and far fewer new cases of metabolic syndrome. For patients at metabolic risk, this makes it a reasonable first-line option. The changes seen with olanzapine were detectable early with simple, inexpensive tests, so routine monitoring with either drug gives clinicians a real opportunity to step in before problems become established.

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