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Original Research Article

A comparative study of the safety of risperidone with olanzapine in patients of new-onset psychosis

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ABSTRACT

Background: Patients with new-onset psychosis are particularly sensitive to adverse effects of antipsychotic medications, which may influence treatment adherence and long-term outcomes. Risperidone and olanzapine are commonly used second-generation antipsychotics with differing safety profiles. This study aimed to compare the safety of risperidone and olanzapine in patients with new-onset psychosis using standardized assessment tools.
Methods: A prospective, randomized, open-label comparative study was conducted in a tertiary care hospital in the sub-Himalayan region of India. Seventy-four consenting adults with newly diagnosed psychosis were randomized into two groups: risperidone (2-8 mg/day, n=36) and olanzapine (5-30 mg/day, n=38). Participants were followed for six months with assessments at baseline, 1, 3, and 6 months. Safety evaluation included clinical adverse effects, biochemical parameters, and extrapyramidal symptoms using the abnormal involuntary movement scale (AIMS) and extrapyramidal symptom rating scale (ESRS).
Results: Baseline characteristics were comparable between groups. Both treatments were associated with weight gain, with a greater metabolic impact observed in the olanzapine group. Significant increases in blood glucose and lipid parameters were noted with olanzapine at six months compared with risperidone ($p<0.05$). Liver enzyme elevations were more frequent with olanzapine but remained clinically manageable. Extrapyramidal symptoms were more pronounced in the risperidone group, particularly during early treatment, as reflected by higher AIMS and ESRS scores. Most adverse effects were mild to moderate and improved over time.
Conclusions: Both risperidone and olanzapine are relatively safe in new-onset psychosis but exhibit distinct adverse-effect profiles. Olanzapine is associated with greater metabolic disturbances, whereas risperidone shows a higher propensity for extrapyramidal symptoms. Individualized drug selection with appropriate monitoring is essential to optimize treatment outcomes.

Keywords: New-onset psychosis, Risperidone, Olanzapine, Extrapyramidal symptoms, Metabolic effects, Antipsychotic safety

INTRODUCTION

Psychosis is a severe psychiatric condition characterized by a disturbed perception of reality. It commonly presents with symptoms such as hallucinations, delusions, disorganized thinking, speech disturbances, and abnormal behaviour, leading to significant impairment in social, occupational, and personal functioning.

Onset of psychosis may be gradual or acute and often represents the initial manifestation of disorders such as schizophrenia, schizoaffective disorder, or mood disorders with psychotic features.[1]

Psychotic disorders, including schizophrenia and related spectrum disorders, are among the most disabling mental illnesses worldwide. The lifetime prevalence of psychotic disorders is estimated to range between 1% and 3%, while schizophrenia affects approximately 0.45-0.6% of the global population. These conditions contribute substantially to disability and are ranked among the leading causes of years lived with disability (YLDs), particularly among young adults.[2]

In India, findings from the National Mental Health Survey (NMHS 2015-16) indicated that schizophrenia and other psychotic disorders affect approximately 0.5% of the adult population, translating to nearly 6.8 million individuals. Community-based studies conducted in different regions of the country have reported prevalence rates of 2-4 per 1000 population and annual incidence rates ranging from 0.35 to 0.45 per 1000 persons.[3]

Although comprehensive epidemiological data from Himachal Pradesh are limited, available regional studies suggest prevalence rates comparable to national estimates. However, the state's challenging mountainous terrain, inadequate mental health infrastructure, and limited accessibility to healthcare services contribute to delayed diagnosis, treatment initiation, and a substantial treatment gap.[4]

First-episode psychosis (FEP) commonly occurs during late adolescence or early adulthood and represents a crucial period for therapeutic intervention. Timely initiation of effective treatment during this phase has been shown to improve long-term clinical outcomes, reduce relapse rates, and enhance overall prognosis.[5]

Despite the benefits of early treatment, individuals experiencing FEP are particularly susceptible to the adverse effects of antipsychotic medications. The occurrence of treatment-related side effects during the initial stages of therapy may negatively affect medication adherence, discourage future treatment-seeking behaviour, and increase the likelihood of progression to chronic illness.[6]

Risperidone is a second-generation (atypical) antipsychotic that exhibits antagonistic activity at dopamine D_2 receptors and serotonin 5-HT_2A receptors, along with affinity for histaminergic and α-adrenergic receptors.[7] It is widely used in the management of schizophrenia, bipolar disorder, and other psychiatric conditions. Its therapeutic efficacy is primarily attributed to modulation of dopaminergic and serotonergic neurotransmission, although interactions with other receptor systems may contribute to its adverse-effect profile.[8]

Common adverse effects associated with risperidone include sedation, weight gain, metabolic disturbances, and extrapyramidal symptoms (EPS) such as acute dystonia, akathisia, drug-induced parkinsonism, and tardive dyskinesia.[9]

Olanzapine is another second-generation antipsychotic with a broad receptor-binding profile, including antagonism at dopaminergic, serotonergic, muscarinic, and histaminergic receptors.[10] It is highly effective in controlling psychotic symptoms but is frequently associated with significant weight gain and metabolic abnormalities. Olanzapine can increase appetite and food intake, leading to hyperphagia and subsequent weight gain. Furthermore, it has been linked to reduced insulin sensitivity and impaired glucose metabolism, particularly among younger patients, thereby increasing the risk of metabolic syndrome and diabetes mellitus.[11]

Although both risperidone and olanzapine are established and effective treatments for psychotic disorders, their tolerability profiles differ considerably. Poor tolerability may result in treatment discontinuation, relapse, reduced adherence, and ultimately poorer clinical outcomes.[12] Extrapyramidal adverse effects, especially akathisia and drug-induced parkinsonism, can significantly impair daily functioning and cause considerable patient distress. In contrast, metabolic adverse effects may develop gradually but are associated with substantial long-term cardiovascular and metabolic risks.[13]

Several studies have compared the efficacy and safety profiles of risperidone and olanzapine. A comprehensive meta-analysis by Leucht et al demonstrated that olanzapine may offer slightly superior efficacy; however, this advantage was accompanied by a greater propensity for weight gain and metabolic complications.[14] Similarly, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study reported comparable efficacy between risperidone and olanzapine, although treatment discontinuation due to adverse effects remained common with both agents.[15]

The present study was undertaken to address the limited evidence regarding the comparative safety of risperidone and olanzapine among patients with new-onset psychosis in the Sub-Himalayan region of India. Using validated assessment tools such as the AIMS and the ESRS, the study aims to objectively evaluate and compare the extrapyramidal adverse-effect profiles of these medications in a drug-naïve population.

Considering the heightened sensitivity of FEP patients to medication-related adverse effects and the challenges associated with long-term monitoring in resource-constrained settings, identifying the safer initial antipsychotic option is of considerable clinical importance. Psychotic disorders impose a substantial burden on individuals, families, and healthcare systems, particularly in rural and underserved regions of the sub-Himalayan belt. As risperidone and olanzapine continue to be widely used as first-line atypical antipsychotics, a comparative assessment of their safety profiles may assist

clinicians in selecting the most appropriate treatment, thereby improving adherence, minimizing adverse effects, and enhancing overall clinical outcomes in early psychosis management.

METHODS

Study setting

The study was carried out in the Department of Psychiatry and Pharmacology, Dr. R.P.G.M.C. Kangra at Tanda, a multispecialty tertiary healthcare facility located in the Kangra valley of Himachal Pradesh in India.

Study design

The study was a prospective, randomized, open label, comparative study.

Study period

The study was conducted from 01-August-2024 to 31-July-2025.

Study duration

The study was started on 01/08/2024 after receiving the due approvals from ethics committee and the CTRI. The study was conducted over a period of six months for enrolment of patients and follow ups were done at the end of first, third, and six months after initiating the treatment.

Sample size

A total of 85 patients were screened, and 74 patients were enrolled and randomized into two groups.

Study population

Consenting adult patients (18+ years) of psychotic illness were selected on the OPD basis.

Inclusion criteria

All the newly diagnosed consenting adult patients of psychosis without any other co-morbidities were included.

Exclusion criteria

The exclusion criteria included patients who were not willing to provide written informed consent, pregnant females, and those already receiving treatment with the study drugs. Patients with known contraindications, refractoriness, or hypersensitivity to the study drugs were also excluded. Additionally, individuals with a known history of heart disease, epilepsy, or other neurological disorders were not included in the study. Patients assessed to have a high risk of suicidal tendencies were also excluded.

Randomization and blinding

Participants were randomized into two groups using a simple random sampling (computer generated numbers) method. Group A (Risperidone group): Tab. Risperidone 2 to 8 mg/day as per the clinical requirement. Group B (Olanzapine group): Tab. Olanzapine 5 to 30 mg/day as per the clinical requirement.

Study procedure (intervention)

After diagnosing patients with new-onset psychosis, they were informed about the study using a patient information sheet, and those who provided written informed consent were enrolled. A detailed history, clinical examination, and necessary investigations were performed. Participants were randomly allocated into two groups using computer-generated random numbers: Group A received risperidone (2-8 mg/day) and Group B received olanzapine (5-30 mg/day), administered after food with dose titration based on clinical response. Baseline investigations were conducted before treatment initiation and repeated at 1, 3, and 6 months during follow-up. The baseline investigations done are Haemoglobin, total leucocyte count, random blood sugar, SGOT, SGPT, S. urea and creatinine, S. sodium and potassium, Lipid profile, weight, AIMS AND ESRS Scale. Patients were monitored through weekly or need-based telephonic contact and were provided with a contact number for reporting discomfort. Any additional investigations advised by physicians were provided free of cost. Adverse drug reactions were recorded during follow-ups, managed appropriately, and reported to the PvPI through the ADR monitoring centre. Safety assessment included monitoring adverse effects, biochemical parameters, and extrapyramidal symptoms using the AIMS and ESRS scales.

Outcome measures

Primary outcomes

It included-Haemoglobin, total leucocyte count, serum sodium and potassium, weight, random blood sugar, lipid profile (cholesterol, triglycerides, LDL, VLDL), liver function tests (SGOT, SGPT) and adverse drug reactions.

Secondary outcome

It included-AIMS score, ESRS score.

Statistical analysis

The data collected was entered into a Microsoft excel spreadsheet regularly and chronologically. Once data collection was completed, the data presented as mean±standard deviation. Student's t-test was used for comparing continuous variables between the two groups. Chi-square or Fisher's exact test was used for comparing the qualitative data between the two groups. Non-parametric variables were analysed using the Wilcoxon

rank-sum test or the Mann–Whitney U test for comparisons across the two study groups. For statistical significance, p value of less than 0.05 was considered statistically significant.

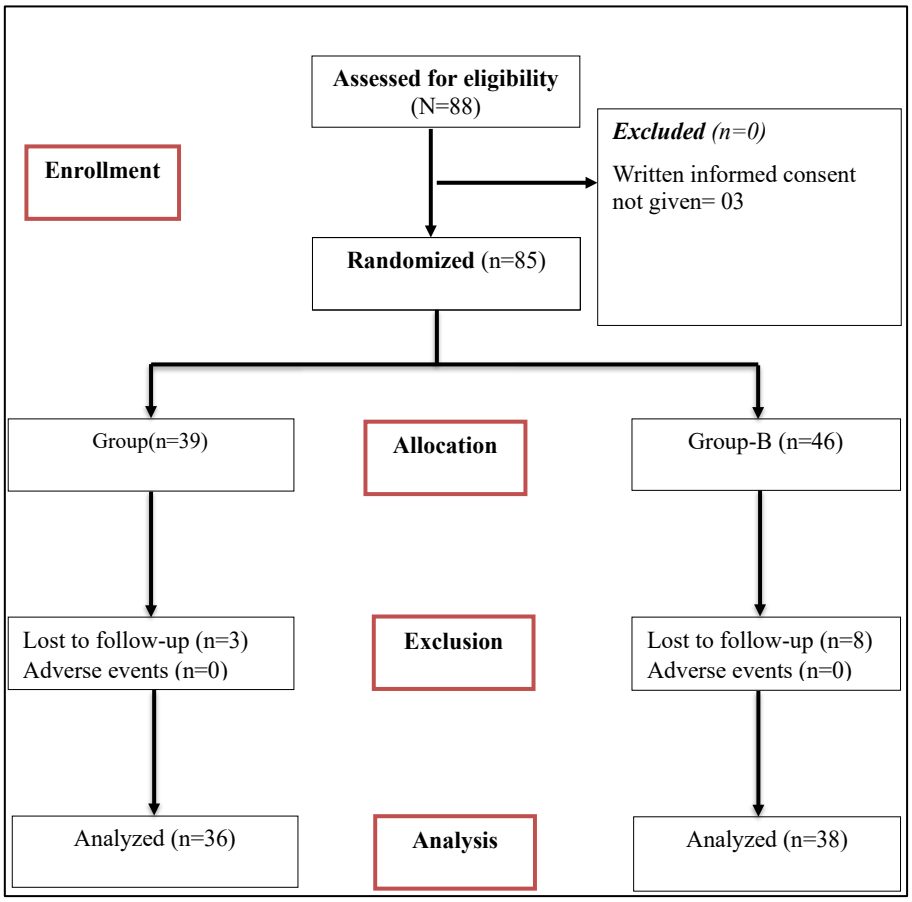

Figure 1: CONSORT flow diagram.

RESULTS

A total of 85 patients with new-onset psychosis were enrolled and randomized into two treatment groups. Of these, 74 participants completed the study and were included in the final analysis (Group A: risperidone, n=36; Group B: olanzapine, n=38). The baseline socio-demographic characteristics such as marital status, residential background, district distribution, age, gender, family history of psychosis, tobacco use, and alcohol consumption were comparable between the two groups, with no statistically significant differences ($p>0.05$). The mean age of participants was 39.1±12.5 years in group A and 37.4±11.0 years in group B ($p=0.52$), and a male predominance was observed in both groups.

Baseline anthropometric and laboratory parameters were similar between the groups. Both treatments were associated with weight gain during the follow-up period. Although the increase was statistically significant within groups, particularly among patients receiving olanzapine, the differences between the two groups at individual follow-up points were not statistically significant. Haemoglobin levels, total leukocyte count, blood pressure, renal function parameters, electrolytes, and most liver function parameters remained within normal limits throughout the study duration, without significant intergroup differences. However, a significant rise in SGOT levels was observed in the olanzapine group at 3 and 6 months compared with baseline values.

Metabolic parameters showed more pronounced changes in patients receiving olanzapine. Random blood sugar levels demonstrated a highly significant increase at 6 months in the olanzapine group compared with both baseline values and the risperidone group ($p<0.001$). Similarly, serum triglycerides, total cholesterol, LDL, and VLDL levels showed significant increases over time in the olanzapine group compared with baseline, suggesting a relatively greater metabolic impact of olanzapine therapy.

Adverse effects were observed in both groups. Constipation was the most frequently reported adverse effect, particularly among patients receiving olanzapine. Increased appetite and sedation were more commonly reported in the risperidone group during the early phase of treatment, while stammering was infrequent in both groups. The proportion of patients reporting no adverse effects increased over time in both groups, indicating possible adaptation to treatment.

Assessment using the AIMS showed that abnormal movements were mainly localized to the orofacial and limb regions in both groups, with slightly greater severity in the risperidone group. Trunk involvement and global severity remained minimal. Evaluation using the ESRS revealed that extrapyramidal symptoms were more pronounced in Group A, especially during early treatment, with gradual improvement over time. In contrast, Group B demonstrated predominantly mild symptoms with better overall tolerability during follow-up.

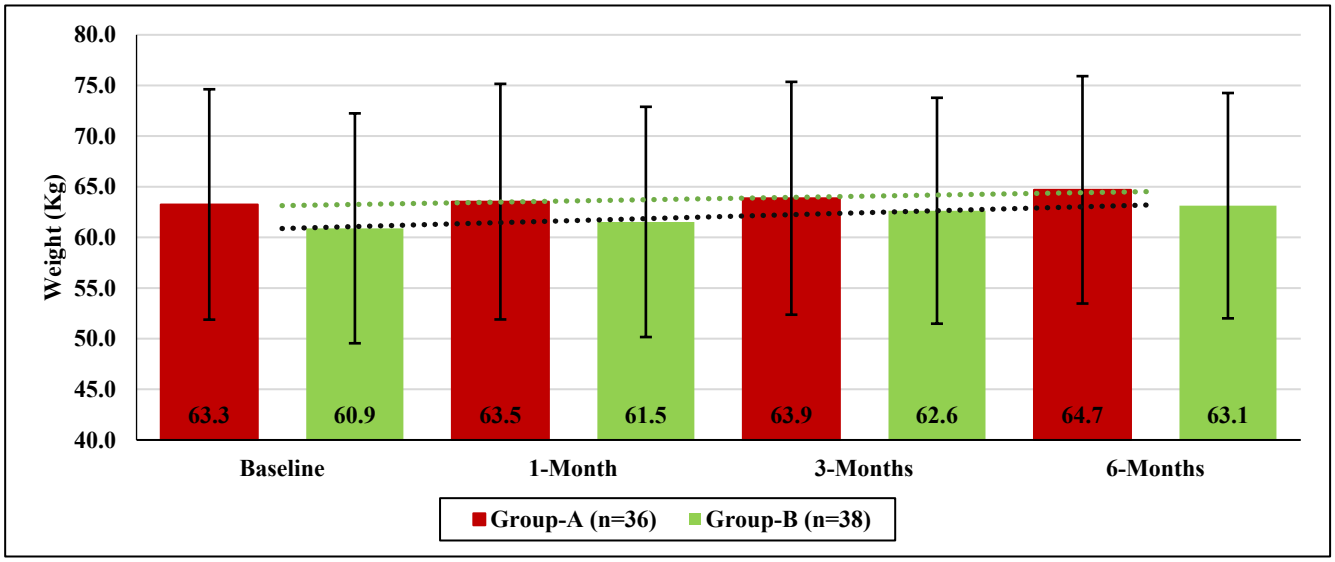

Figure 2: Comparison of weight between two groups.

Table 1: Comparison of aspartate aminotransferase levels between two groups.

SGOT (U/L)	Group A, (n=36)	Group B, (n=38)	P value#
Baseline	24.1±7	24±8.5	0.99
1-month	25.4±8.1	25.1±7.9	0.84
3-months	24.9±8.3	27.3±8.4	0.22
6-months	26±7.8	29.2±8.6	0.1
P value#, baseline vs 1-month, 3-months, 6-months	0.08, 0.30, 0.07	0.1, 0.001*, 0.001*	

Data expressed as mean±SD, #Student's t-test, *Statistically significant

Table 2: Comparison of alanine aminotransferase levels between two groups.

SGPT (U/L)	Group A, (n=36)	Group B, (n=38)	P value#
Baseline	24.1±8.2	25.2±8.9	0.57
1-month	24.3±7.6	25.9±8.4	0.39
3-months	24.9±7.7	27.5±7.7	0.15
6-months	25.1±7.8	29±7.6	0.03*
P value#, baseline vs 1-month, 3-months, 6-months	0.54, 0.13, 0.1	0.12, 0.04*, 0.03*	

Data expressed as mean±SD, #Student's t-test, * Statistically significant

Table 3: Comparison of random blood sugar levels between two groups.

Random Blood sugar (mg/dl)	Group A, (n=36)	Group B, (n=38)	P value#
Baseline	102±18.2	105.6±18.3	0.39
1-month	104.2±17.7	106.4±23.1	0.64
3-months	105.6±10.2	110.1±20.7	0.25
6-months	106.6±17.2	120.9±13.1	0.001*
P value#, baseline vs 1-month, 3-months, 6-months	0.62, 0.39, 0.34	0.87, 0.24, 0.001*	

Data expressed as mean±SD, #Student's t-test, *Statistically significant

Table 4: Comparison of serum triglyceride levels between two groups.

Serum triglyceride (mg/dl)	Group A, (n=36)	Group B, (n=38)	P value#
Baseline	139.9±21.3	135.6±21.7	0.39
1-month	141.2±21.0	139.8±21.9	0.78
3-months	142.0±22.1	143.7±21.9	0.74
6-months	145.3±27.1	148.5±21.2	0.58
P value#, baseline vs 1-month, 3-months, 6-months	0.32, 0.34, 0.11	0.001*, 0.001*, 0.001*	

Data expressed as mean±SD, #Student's t-test, * Statistically significant

Table 5: Comparison of serum cholesterol levels between two groups.

Serum cholesterol (mg/dl)	Group A, (n=36)	Group B, (n=38)	P value#
Baseline	201.1±25.6	190.5±25.5	0.08
1-month	198.2±25.6	192.3±26.4	0.33
3-months	201.9±25.4	198.1±22.3	0.49
6-months	203.4±26.4	202.3±24.8	0.85
P value#, baseline vs 1-month, 3-months, 6-months	0.12, 0.60, 0.12	0.03*, 0.02*, 0.01*	

Data expressed as mean±SD, #Student's t-test, *Statistically significant.

Table 6: Comparison of serum LDL levels between two groups.

Serum LDL (mg/dl)	Group A, (n=36)	Group B, (n=38)	P value#
Baseline	91.9±22.9	83.7±16.1	0.08
1-month	92.5±22.8	84.8±15.4	0.09
3-months	92.9±20.7	86.6±14.8	0.13
6-months	93.5±18.5	89.4±12.9	0.27
P value#, baseline vs 1-month, 3-months, 6-months	0.2, 0.26, 0.15	0.04*, 0.04*, 0.02*	

Data expressed as mean±SD, #Student's t-test, *Statistically significant

Table 7: Comparison of serum VLDL levels between two groups.

Serum VLDL (mg/dl)	Group A, (n=36)	Group B, (n=38)	P value#
Baseline	23±5.1	23.7±4.5	0.54
1-month	23.4±6.4	24.7±5.5	0.34
3-months	23.4±5.8	26.5±4.2	0.01*
6-months	23.9±6.3	28.4±5.7	0.001*
P value#, baseline vs 1-month, 3-months, 6-months	0.57, 0.49, 0.22	0.03*, 0.03*, 0.02*	

Data expressed as mean±SD, #Student's t-test, *Statistically significant

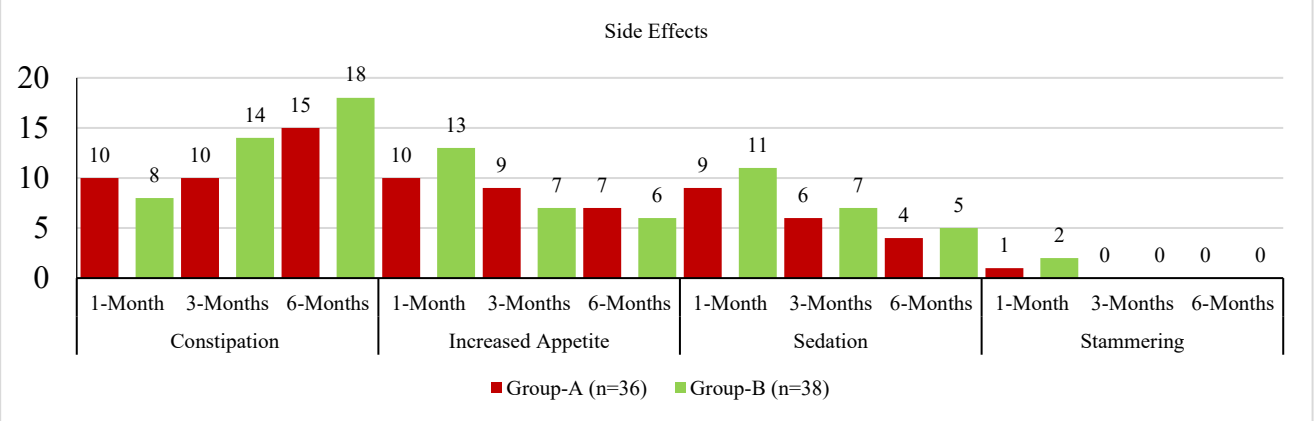

Figure 3: Comparison of side-effects between two groups.

DISCUSSION

The present study evaluated the comparative safety of risperidone and olanzapine in patients with new-onset psychosis over a six-month follow-up period. The two treatment groups were comparable with respect to baseline sociodemographic characteristics, including age, gender distribution, family history of psychosis, marital status, and substance use patterns. This similarity supports the adequacy of randomization and reduces the likelihood of baseline confounding, consistent with previous comparative studies of second-generation antipsychotics conducted in similar patient populations.[16,17]

Both medications were associated with progressive weight gain during treatment, with olanzapine demonstrating a tendency toward earlier increases. However, the differences between groups did not reach statistical significance. These findings are broadly consistent with existing literature indicating that atypical antipsychotics, particularly olanzapine, are associated with clinically meaningful weight gain through mechanisms involving appetite stimulation and metabolic dysregulation.[18,19] The absence of significant intergroup differences in the present study may reflect the modest sample size, interindividual metabolic variability, or the relatively short duration of follow-up.

Haematological parameters, including haemoglobin and total leukocyte count, remained stable throughout the study in both groups, suggesting a favourable haematological safety profile. Similar observations have been reported in earlier prospective and observational studies evaluating the safety of risperidone and olanzapine.[16,17] Renal function parameters also remained within normal limits without clinically significant changes, indicating minimal nephrotoxic potential in patients without underlying renal impairment.[20]

Cardiovascular parameters, including systolic and diastolic blood pressure, showed no significant differences between the two treatment groups over time. These findings support the short-term cardiovascular safety of both medications and are in agreement with prior studies.[16,21] Nevertheless, previous reports have suggested that olanzapine may contribute to blood pressure increases in certain populations, highlighting the role of individual susceptibility and treatment duration in determining cardiovascular risk.[22]

Liver function tests revealed significant increases in transaminase levels in patients receiving olanzapine, whereas changes in the risperidone group were minimal. Although statistically significant, these elevations were generally mild and clinically manageable. Earlier studies have similarly reported transient liver enzyme elevations with atypical antipsychotics without evidence of severe hepatotoxicity.[23,24] However, retrospective analyses have suggested a relatively higher frequency of hepatic enzyme abnormalities with olanzapine compared with risperidone, underscoring the importance of periodic monitoring during therapy.[25,26]

Serum electrolyte levels remained stable in both groups, with no clinically significant abnormalities observed. This finding is consistent with previous research indicating minimal electrolyte disturbances with atypical antipsychotics.[27] Nonetheless, isolated reports of hyponatremia and hypokalaemia emphasize the need for vigilance in susceptible individuals.[28,29]

Metabolic effects differed more clearly between the two medications. Olanzapine was associated with significant increases in blood glucose levels at six months compared with baseline and the risperidone group, consistent with evidence linking olanzapine to insulin resistance and metabolic syndrome risk.[17,18] Similarly, lipid parameters-including triglycerides, total cholesterol, LDL, and VLDL-showed greater increases with olanzapine, reinforcing its higher metabolic liability compared with risperidone.[17,21,30] These metabolic changes are clinically important given their association with long-term cardiovascular morbidity.

Regarding adverse effects, constipation, increased appetite, and sedation were commonly observed in both groups, with slightly higher frequencies in patients receiving olanzapine. These findings align with meta-analytic evidence describing the tolerability profiles of atypical antipsychotics.[18] Stammering was infrequent and transient, suggesting limited clinical significance.

Extrapyramidal symptom assessment using AIMS and ESRS demonstrated a greater burden of movement disorders in the risperidone group, particularly affecting orofacial and limb regions, while trunk involvement remained minimal in both groups. This observation is consistent with the pharmacological profile of risperidone, which has relatively stronger dopamine D2 receptor antagonism compared with olanzapine.[20,31] ESRS findings further indicated higher severity of akathisia, dystonia, dyskinesia, and parkinsonism with risperidone, particularly during early treatment phases, whereas olanzapine demonstrated better tolerability. Similar patterns have been reported in randomized trials and observational studies,[32,33] although some systematic reviews have noted minimal differences between the two agents, suggesting that dose, duration, and patient-specific factors also influence extrapyramidal risk.[34,35]

Overall, the findings of this study suggest that both risperidone and olanzapine are relatively safe options for the management of new-onset psychosis but are associated with distinct adverse-effect profiles. Olanzapine appears to confer greater metabolic and hepatic risk, whereas risperidone is associated with a higher likelihood of extrapyramidal symptoms. These differences underscore the importance of individualized antipsychotic selection based on patient characteristics, comorbidities, and monitoring requirements.

Strengths and limitations

This study has several strengths, including its prospective comparative design with six-month follow-up, enrolment of drug-naïve patients with new-onset psychosis, and the use of validated assessment tools (AIMS and ESRS), which improved the reliability of safety evaluation. The comprehensive assessment of anthropometric, metabolic, biochemical, and clinical parameters further enabled a holistic comparison between risperidone and olanzapine. Comparable baseline characteristics between groups also enhanced internal validity.

However, limitations include a modest sample size, single-center design, and relatively short follow-up duration, which may restrict generalizability and the ability to detect long-term adverse outcomes. Lack of blinding may have introduced observer bias, and lifestyle factors were not strictly controlled. Additionally, variations in dosing and treatment adherence were not extensively evaluated.

Despite these limitations, the findings provide clinically meaningful insights into the comparative safety profiles of risperidone and olanzapine in patients with new-onset psychosis and may support individualized treatment selection.

CONCLUSION

The study demonstrates that although both risperidone and olanzapine are effective in the management of new-onset psychosis, their safety profiles differ considerably. Olanzapine is associated with greater metabolic adverse effects, particularly weight gain, dyslipidaemia, and hyperglycaemia, whereas risperidone shows a higher propensity for extrapyramidal symptoms. These differences highlight the importance of thorough baseline assessment and ongoing monitoring, along with individualized treatment selection based on patient-specific risk factors. Overall, the findings add to existing evidence on the comparative safety of antipsychotic therapy and provide clinically relevant guidance for optimizing treatment decisions in patients with psychosis.

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