**International Journal of Medical and Pharmaceutical Research**

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

# Adverse Drug Reactions to Aripiprazole and Risperidone in Schizophrenia: A Comparative Cross-Sectional Study

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OPEN ACCESS

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*Received: 12-06-2026*
*Accepted: 15-07-2026*
*Available online:31-07-2026*



## ABSTRACT

**Background**: Long-term antipsychotic therapy is an essential part of treatment for schizophrenia. Hence, the safety and tolerability of these medications are important determinants of treatment adherence and clinical outcomes. Risperidone and aripiprazole are among the most commonly prescribed second-generation antipsychotics. The differences in their adverse drug reaction (ADR) profiles are not extensively reported in the Indian population.
**Objectives**: To estimate and compare the frequency and severity of adverse drug reactions among patients with schizophrenia receiving aripiprazole or risperidone monotherapy.
**Methods**: A descriptive cross-sectional observational study was conducted in the Psychiatry Outpatient Department of a tertiary care hospital between January and March 2025. Adult patients diagnosed with schizophrenia according to ICD-10 criteria and receiving monotherapy with either aripiprazole or risperidone were included. ADRs were assessed using a predesigned case record form and graded according to the Hartwig and Siegel Severity Assessment Scale.
**Results**: A total of 120 patients (70 receiving risperidone and 50 receiving aripiprazole) were enrolled, and 130 ADRs were documented. Headache (21.54%), fatigue (15.38%), drowsiness (11.54%), weakness (8.46%), and weight gain (7.69%) were the most frequently reported ADRs. Aripiprazole was associated with a significantly higher frequency of fatigue (p=0.046), whereas drowsiness (p=0.002) and nausea (p=0.011) were significantly more common with risperidone. Weight gain was observed predominantly with aripiprazole (9/10 cases), while amenorrhea and erectile dysfunction occurred almost exclusively with risperidone.
**Conclusion**: Aripiprazole and risperidone were generally well tolerated; however, their distinct adverse drug reaction profiles should be carefully considered when selecting treatment for individual patients.

***Keywords***: *Schizophrenia; Adverse drug reactions; Aripiprazole; Risperidone; Second-generation antipsychotics; Drug safety; Tolerability.*

## INTRODUCTION

Schizophrenia is a chronic and disabling psychiatric disorder that substantially contributes to the global burden of disease through persistent symptoms, functional impairment, and reduced quality of life. According to the National Mental Health Survey of India (2023), schizophrenia spectrum disorders have a lifetime prevalence of 1.41% and a current prevalence of 0.42% in the Indian population, highlighting the considerable public health importance of these disorders in the country. (Hegde et al., 2023) Long-term maintenance treatment with antipsychotic medications remains the cornerstone of

schizophrenia management. Although lifelong treatment may not be necessary for every individual, the majority of patients require prolonged or continuous antipsychotic therapy to maintain symptom remission, prevent relapse, and improve psychosocial functioning. (Harrow et al., 2012) Consequently, the long-term safety and tolerability of antipsychotic medications become critical determinants of treatment adherence and clinical outcomes.

First-generation antipsychotics (FGAs), while effective in controlling psychotic symptoms, are frequently associated with extrapyramidal symptoms (EPS), including parkinsonism, dystonia, akathisia, and tardive dyskinesia. (Leucht et al., 2013) The introduction of second-generation antipsychotics (SGAs) represented a major advance in schizophrenia treatment because of their lower propensity to cause EPS. However, subsequent experience demonstrated that many SGAs are associated with significant metabolic adverse effects, including weight gain, dyslipidaemia, glucose intolerance, and increased cardiovascular risk. (Burschinski et al., 2023) These adverse effects contribute substantially to poor medication adherence and increased physical morbidity among patients with schizophrenia.

Among the SGAs, risperidone and aripiprazole are among the most commonly prescribed agents owing to their favourable balance between efficacy and tolerability. Both drugs have a relatively lower risk of extrapyramidal symptoms and metabolic complications compared with several other antipsychotics. (Pillinger et al., 2020) Nevertheless, important differences exist in their adverse effect profiles. Studies have reported that nearly 68% of patients receiving risperidone experience at least one adverse drug reaction, with hyperprolactinaemia, clinically significant weight gain, and extrapyramidal symptoms being the most frequently observed adverse effects. (Alladi et al., 2017) In contrast, aripiprazole demonstrates a more favourable metabolic and endocrine profile, with approximately one-third of patients experiencing predominantly mild adverse drug reactions such as akathisia, constipation, palpitations, insomnia, and extrapyramidal symptoms. (Mao et al., 2024)

Evidence from comparative clinical trials and meta-analyses further highlights these differences. Aripiprazole has consistently demonstrated good tolerability, with most adverse events being mild to moderate and low treatment discontinuation rates. Compared with risperidone, it has been associated with a lower risk of hyperprolactinaemia, sexual dysfunction, sedation, cholesterol elevation, and, in several studies, reduced weight gain. Conversely, risperidone has been associated with greater prolactin elevation, menstrual disturbances, sexual adverse effects, and rigidity, although both medications exhibit comparable efficacy and similar rates of extrapyramidal symptoms in many studies.

Given that most individuals with schizophrenia require long-term antipsychotic treatment, understanding the comparative adverse effect profiles of commonly prescribed medications is essential for individualized treatment selection, improving medication adherence, and optimizing long-term outcomes. However, evidence from Indian clinical settings comparing the adverse drug reactions associated with risperidone and aripiprazole remains limited. Therefore, the present study was undertaken to estimate and compare the frequency and severity of adverse drug reactions among patients with schizophrenia receiving aripiprazole or risperidone.

## METHODOLOGY

A descriptive cross-sectional observational study was conducted in the Psychiatry Outpatient Department (OPD) over a two-month period from January 2025 to March 2025. Adult men and women diagnosed with schizophrenia according to the ICD-10 diagnostic criteria and receiving monotherapy with either risperidone or haloperidol were included in the study. Pregnant and lactating women, patients receiving treatment for other psychiatric disorders, and those with medical conditions likely to cause adverse effects were excluded.

The sample size was calculated using Open epi version 3.01, assuming an expected prevalence of the outcome variable of 20.68%, with a 95% confidence level and an absolute precision of 7.5%.(Garrido-Sánchez et al., 2022; Sullivan et al., 2009) Consecutive eligible patients attending the Psychiatry OPD on three days per week during the study period were recruited until the required sample size was achieved.

Data were collected using a predesigned case record form to obtain sociodemographic and clinical information. Adverse drug reactions (ADRs) were assessed using the Hartwig and Siegel Severity Assessment Scale. Based on the severity grading of this scale, ADRs were classified as mild, moderate, or severe. Participants identified with ADRs were referred to a psychiatrist or physician, as appropriate, for further evaluation and management.

## RESULTS

A total of 120 patients diagnosed with schizophrenia were included in the study, of whom 70 were receiving risperidone and 50 were receiving aripiprazole as monotherapy. Overall, 130 adverse drug reactions (ADRs) were documented, indicating that several patients experienced more than one ADR during the study period.

The age of the participants ranged from 18 to 60 years and they were categorized into three groups: 18–31 years, 32–45 years, and 46–60 years. The highest number of ADRs was observed in the 46–60-year age group (52.3%), followed by the 32–45-year group (33.1%), while the youngest age group (18–31 years) accounted for 14.6% of all reported ADRs. General

ADRs did not differ significantly across age groups ($\chi^2$=7.83, p=0.097), whereas central nervous system (CNS) adverse effects demonstrated a statistically significant association with age ($\chi^2$=43.24, p=0.0001). Headache was the most frequently reported ADR among older participants, while drowsiness was predominantly observed in the 32–45-year age group. Among the 120 participants, 52 were males and 68 were females. Females accounted for a greater proportion of ADRs than males. Significant sex-based differences were observed in the distribution of general ADRs ($\chi^2$=35.79, p=0.0001) and CNS-related ADRs ($\chi^2$=54.57, p=0.0001). Fatigue and weakness were reported more frequently among females, whereas drowsiness was more common among males in the middle age group.

Headache was the most commonly reported adverse reaction, accounting for 21.54% of all ADRs (28/130), followed by fatigue (15.38%), drowsiness (11.54%), weakness (8.46%), weight gain (7.69%), sedation (6.92%), tremor (6.15%), giddiness (5.38%) and somnolence (4.62%). Less frequently encountered ADRs included irregular menses (2.31%), amenorrhea (2.31%), nausea (1.54%), increased appetite (1.54%), memory impairment (1.54%), palpitations (1.54%) and erectile dysfunction (1.54%). Differences were observed in the ADR profiles of aripiprazole and risperidone. Of the 130 ADRs reported, 57 (43.8%) were associated with aripiprazole and 73 (56.2%) with risperidone. Fatigue was the most common ADR associated with aripiprazole, constituting 24.56% of ADRs reported with the drug, whereas headache was the most frequent ADR among risperidone-treated patients (24.66%). Compared with risperidone, aripiprazole was associated with a significantly higher frequency of fatigue ($\chi^2$=6.16, p=0.046). In contrast, drowsiness ($\chi^2$=18.71, p=0.002) and nausea ($\chi^2$=11.04, p=0.011) were reported significantly more often with risperidone. Weight gain was observed predominantly with aripiprazole, accounting for 9 of the 10 reported cases, whereas only one case was documented with risperidone. Sexual and reproductive adverse effects, including amenorrhea and erectile dysfunction, were observed almost exclusively among patients receiving risperidone, although statistical significance could not be established because of the small number of events.

Severity assessment using the Hartwig and Siegel Severity Scale demonstrated that the majority of ADRs were mild in nature. Of the 130 reported ADRs, 125 (96.15%) were categorized as mild (Levels 1 and 2), while only five (3.85%) were of moderate severity (Levels 3 and 4). No severe ADRs (Levels 5–7) were encountered. Moderate ADRs were limited to tremor (four cases) and palpitations (one case). The severity profile was comparable between the two drugs, with 54 of 57 ADRs (94.7%) associated with aripiprazole and 71 of 73 ADRs (97.3%) associated with risperidone being classified as mild, indicating that both medications were generally well tolerated in the study population.

## DISCUSSION

The present study compared the adverse drug reaction (ADR) profiles of aripiprazole and risperidone in patients with schizophrenia attending a tertiary care hospital. A total of 130 ADRs were identified among 120 participants, with most reactions being mild in severity. Headache, fatigue and drowsiness were the most frequently reported adverse events. Although both antipsychotics demonstrated acceptable tolerability, they exhibited different ADR patterns. Fatigue was significantly more frequent with aripiprazole, whereas drowsiness and nausea were significantly more common with risperidone. Age-wise analysis revealed that the highest proportion of ADRs occurred in patients aged 46–60 years, while the lowest frequency was observed among younger adults. Central nervous system adverse effects showed a significant association with age, with headache occurring predominantly in older participants and drowsiness being more frequent among individuals aged 32–45 years. Advancing age is known to influence pharmacokinetics and pharmacodynamics, increasing susceptibility to adverse drug reactions, particularly those related to the nervous system.( Ngcobo N. N. ,2025) Female participants experienced a greater proportion of ADRs than males, with significant differences observed for both general and central nervous system adverse effects. Fatigue and weakness were more frequently reported among females, whereas drowsiness predominated among males in the middle age group. Although sex-related differences in antipsychotic pharmacokinetics, hormonal influences and body composition have been proposed as potential contributors to differential tolerability, evidence remains inconsistent across studies. ( Aichhorn et al. 2006) Headache was the commonest ADR in the overall study population, accounting for 21.54% of all reported reactions, followed by fatigue, drowsiness and weakness. These findings are broadly comparable with previous studies evaluating the tolerability of second-generation antipsychotics. Previous research reported fatigability, weight gain and drowsiness among the most frequently encountered adverse effects during acute treatment with aripiprazole and risperidone.(Garrido-Sánchez et al., 2022) Although the exact frequencies differed from those observed in the present study, the overall pattern indicates that nonspecific neurological and constitutional symptoms constitute a substantial proportion of ADRs associated with these medications.

Comparison of individual drug profiles demonstrated important differences in tolerability. Fatigue was the predominant ADR associated with aripiprazole and occurred significantly more frequently than with risperidone. In contrast, risperidone was associated with significantly higher frequencies of drowsiness and nausea. Potkin et al. reported that aripiprazole was generally well tolerated, with adverse events being predominantly mild to moderate and comparable with placebo for extrapyramidal symptoms and electrocardiographic abnormalities. (Potkin et al.,2003) Similarly, the present study found no severe ADRs associated with aripiprazole, supporting its favourable overall tolerability profile. An interesting finding of the present study was that weight gain was observed predominantly among patients receiving aripiprazole, with nine of the ten reported cases occurring in this treatment group. This observation differs from much of the published literature. Bourgon et al. found no statistically significant differences in weight change between the two drugs.(Vázquez-Bourgon et

al., 2022) Likewise, the meta-analysis by Leucht et al. suggested that aripiprazole is generally associated with less weight gain than several other second-generation antipsychotics, including risperidone.(Leucht et al., 2013) The discrepancy between our findings and previous evidence may be attributable to the relatively small sample size, cross-sectional study design, and presence of differences in baseline body weight, dietary habits, or other unmeasured confounding variables.

Sexual and reproductive adverse effects were observed predominantly among patients receiving risperidone. Amenorrhea, erectile dysfunction and irregular menstrual cycles were largely confined to this group, although the absolute number of cases was small. These findings are consistent with previous studies demonstrating a greater propensity of risperidone to produce hyperprolactinemia-related adverse effects. Garrido-Sánchez et al. reported significantly higher frequencies of amenorrhea, reduced sexual desire, erectile dysfunction and ejaculatory dysfunction among risperidone-treated patients.(Garrido-Sánchez et al., 2022) Similarly, Koch et al. demonstrated substantially higher prolactin concentrations and greater rates of prolactin-related adverse events with risperidone compared with aripiprazole.(Koch et al., 2023) The pharmacological basis for this difference is well established, as risperidone acts primarily as a dopamine $D_2$ receptor antagonist, whereas aripiprazole functions as a partial $D_2$ receptor agonist and is therefore associated with a lower risk of sustained prolactin elevation.(Raghuthaman et al., 2015) Severity assessment using the Hartwig and Siegel Scale demonstrated that 96.15% of ADRs were mild, while only 3.85% were of moderate severity. No severe ADRs were encountered, and none required treatment discontinuation. These findings closely resemble those reported by Potkin et al., who observed that most adverse events associated with aripiprazole were mild to moderate and rarely necessitated withdrawal from treatment. (Potkin etal.,2003)

The present study has certain limitations. Its cross-sectional design precluded assessment of temporal changes in ADRs, dose modifications and long-term outcomes. Information regarding treatment duration, cumulative drug exposure and baseline metabolic parameters was not incorporated into the analysis given the limited scope of study. The relatively modest sample size and single-centre setting also limit the generalizability of the findings. Furthermore, the small number of uncommon ADRs reduced the statistical power to detect differences for certain adverse effects.

## CONCLUSION

Overall, the findings suggest that both aripiprazole and risperidone were generally well tolerated, with predominantly mild adverse drug reactions. Rather than indicating the overall superiority of one drug, these findings emphasize that the choice of antipsychotic should be individualized according to patient characteristics, anticipated adverse effects and clinical priorities.

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