

# Comparative Evaluation of Typical Antipsychotic Haloperidol with Atypical Antipsychotics Olanzapine, Risperidone and Aripiprazole in the Treatment of Stable Schizophrenia in a Tertiary Care Teaching Hospital at Dehradun, Uttarakhand, India: A Randomised Clinical Trial

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## ABSTRACT

**Introduction:** Schizophrenia, a chronic psychiatric disorder, significantly impacts patients' quality of life through positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., social withdrawal, emotional blunting) and cognitive impairments. The pharmacological treatment landscape has evolved from First-Generation Antipsychotics (FGAs) like haloperidol to Second-Generation Antipsychotics (SGAs), such as olanzapine, risperidone and aripiprazole, which aim to improve therapeutic outcomes while minimising adverse effects. However, comparative evaluations of efficacy and safety among these agents remain critical, especially in the Indian context.

**Aim:** To compare the therapeutic efficacy and safety of the FGA haloperidol with the SGAs olanzapine, risperidone and aripiprazole in the management of stable schizophrenia.

**Materials and Methods:** This randomised, clinical open-label, prospective study was conducted for one year which included 98 stable schizophrenia patients diagnosed according to the International Classification of Diseases -10 criteria. Participants were divided into four groups receiving haloperidol (n=24), olanzapine (n=25), risperidone (n=25), or aripiprazole (n=24). Psychometric assessments were performed using the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Symptoms Scale (PANSS), Clinical Global Impression (CGI), and

Calgary Depression Scale for Schizophrenia (CDSS) at baseline and follow-up visits over 16 weeks. Adverse Drug Reactions (ADRs) were monitored using the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment Scale. Statistical analysis included paired t-tests and Analysis of Variance (ANOVA), with significance set at p-value <0.05.

**Results:** Olanzapine demonstrated the greatest efficacy, with significant improvements in BPRS and PANSS scores (p-value <0.0001), followed by risperidone and aripiprazole. Haloperidol showed efficacy in controlling positive symptoms but was less effective for negative and cognitive symptoms. ADRs were most frequent with haloperidol (57 events), primarily Extrapyramidal Symptoms (EPS), while SGAs exhibited better tolerability profiles with olanzapine showing the least ADRs (27 events). Weight gain and increased appetite were common among SGAs, whereas aripiprazole had the lowest metabolic disturbances.

**Conclusion:** The study underscores the superior efficacy and safety profiles of SGAs, particularly olanzapine and risperidone, in managing stable schizophrenia. Haloperidol remains useful for acute symptom control but is less suitable for long-term therapy due to its adverse effects. These findings reinforce the importance of personalised treatment strategies to optimise schizophrenia management and improve patient outcomes.

**Keywords:** Adverse effects, Effects, Safety

## INTRODUCTION

Health, as defined by the WHO, is "a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" [1]. Mental health is integral to overall health, with the WHO defining it as "a state of wellbeing in which an individual realises their abilities, can cope with the normal stresses of life, can work productively and contribute to their community" [2].

Globally, mental health disorders contribute significantly to the disease burden, with schizophrenia being one of the most debilitating conditions. It affects approximately 24 million people worldwide, with a global prevalence of 0.3-0.7% among adults and a lifetime prevalence of nearly 1% [3,4]. This disorder commonly manifests in late adolescence or early adulthood, significantly impacting social and occupational functioning. The early onset, chronicity and disabling nature of schizophrenia impose substantial social and economic costs due to reduced

productivity, high healthcare expenditures and dependency on caregivers [5,6].

In India, schizophrenia affects an estimated 3-5 per 1,000 individuals, with a higher prevalence in urban areas. According to the National Mental Health Survey 2015-16, the prevalence of schizophrenia and psychotic disorders in the Indian population is approximately 1.4%, with significant treatment gaps, especially in rural regions [7,8]. Factors such as stigma, limited access to mental healthcare and socio-economic challenges exacerbate the burden of the disease [9,10].

Pharmacological management remains the cornerstone of schizophrenia treatment. FGAs such as haloperidol primarily target dopamine D2 receptors and are effective against positive symptoms, including hallucinations and delusions. However, their use is often limited by adverse effects such as EPS, tardive dyskinesia and hyperprolactinaemia [11,12]. The introduction of SGAs, including

olanzapine, risperidone and aripiprazole, has significantly advanced schizophrenia management. SGAs target both dopamine and serotonin receptors, improving efficacy against both positive and negative symptoms, with a lower risk of neurological side-effects. These SGAs also show promise in addressing cognitive impairments associated with schizophrenia [13,14].

Despite these advancements, challenges such as treatment resistance and adverse effects persist. No single agent can be deemed ideal or perfect, making it difficult for a prescriber to choose among the many available options. Despite the vast literature on this topic, a study was needed to further expand the knowledge of SGAs in comparison to one another as well as to FGAs. The present study, aimed to provide evidence-based insights into managing stable schizophrenia in the Indian context.

## MATERIALS AND METHODS

It was a randomised, clinical open-label, prospective study. Prior to the initiation of the study, approval from the Institutional Ethics/Research Committee (Approval No.: SGR/Rec/56/14, dated 21.11.2014) was obtained. The study was conducted at Shri Guru Ram Rai Medical College, Hospital and Research Centre, Dehradun, Uttarakhand, India, from 1 January 2015 to 31 December 2015. The trial was registered with CTRI (CTRI No: CTRI/2020/01/022712). Written informed consent was obtained from each legal guardian of the schizophrenic patients after a complete explanation of the elements contained in the research protocol. A total of 98 stable schizophrenic patients, diagnosed according to ICD-10 criteria, attending the psychiatry Outpatient Department (OPD), were included in the study.

**Inclusion criteria:** Patients were included based on the following criteria: (a) both genders (male and female); (b) age ranging from 18 to 70 years; (c) stable schizophrenic patients with an initial BPRS score of  $\geq 24$  and a Clinical Global Impression Severity Rating Scale score of  $\geq 4$ ; (d) patients who had routine haematological laboratory investigations at the time of inclusion that were within normal range (to rule out any co-morbid/systemic illness).

**Exclusion criteria:** Patients were excluded based on the following criteria: (a) age less than 18 years or more than 70 years; (b) pregnant or lactating women; (c) acute emergencies; (d) history of hypersensitivity or allergy to any of the drugs included in the study; (e) impaired renal or hepatic function; or (f) a history of any systemic illness.

### Sample size calculation:

Sample size was calculated using following simple formula:

$$n = \frac{Z^2 p (1-p)}{d^2}$$

Where, n is the sample size, 'Z' is the statistic corresponding to level of confidence, 'P' is expected prevalence and d is precision (corresponding to effect size).

### Value used were:

Z=1.96 (for 95% level of confidence)

Prevalence: 0.5 (3-5/1000 population India, as quoted in introduction part)

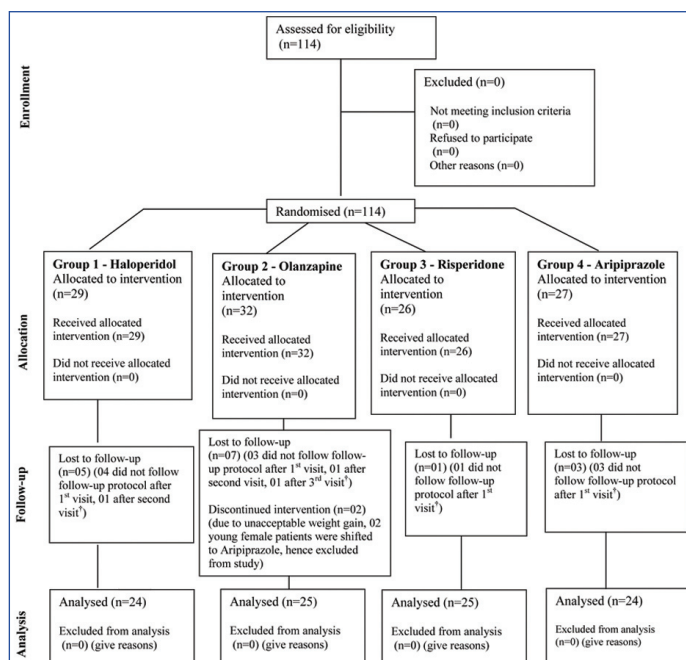
d=0.1 (for P~0.5)

$n = 3.8416 \times 0.5(1-0.5) / 0.1 \times 0.1 = 0.9604 / 0.01 = 96$

**Patient selection:** Selection was based on ICD-10 criteria [15] for the confirmation of the diagnosis of schizophrenia.

**Randomisation:** To eliminate selection bias and to randomly assign patients to four study groups, a random allocation table was prepared in advance using Microsoft Excel for the allocation of included patients to the four study groups.

**Study groups:** A total of 98 subjects were randomly included in four study groups according to the drug treatment provided: Group I: Haloperidol (n=24); Group II: Olanzapine (n=25); Group III: Risperidone (n=25); Group IV: Aripiprazole (n=24) [Table/Fig-1].



[Table/Fig-1]: CONSORT's flowchart.

<sup>1</sup>Patients consented but visited as per his/her ease, not according to study protocol

**Psychometric evaluation:** Patients were assessed and evaluated at each visit using the following psychiatric scales:

- BPRS [16];
- PANSS [17];
- CGI [18];
- CDSS [19].

**BPRS:** The BPRS includes 18 items that address somatic concerns, anxiety, emotional withdrawal, conceptual disorganisation, etc. Items on the BPRS are rated on a 7-point scale anchored as follows: not present, very mild, mild, moderate, moderately severe, severe, and extremely severe. The total score is the simple sum of the items. The scoring system uses values within a total score range of 18-126, with higher scores indicating more severe psychopathology.

**PANSS:** The PANSS includes three scales and 30 items: seven items make up the Positive scale, the next seven items make up the Negative scale, and 16 items make up the General Psychopathology scale. Individual items are scored with values ranging from 1 to 7. Scores above one indicate that a clinical symptom is present and ratings of 2-7 indicate increasing severity. The potential range for the positive and negative scales is 7-49, while the range for the General Psychopathology scale is 16-112.

**CGI:** CGI scale consists of three global subscales. The first subscale, Severity of Illness (SI), assesses the clinician's impression of the patient's current illness state. Scores on the SI subscale range from 1 (not ill at all) to 7 (among the most extremely ill). The next subscale, Global Improvement (GI), evaluates the patient's improvement or worsening from baseline. The GI subscale also ranges from 1 (very much improved) to 7 (very much worse). The third subscale, the Efficacy Index (EI), is a ratio of benefit to risk that attempts to assess the overall efficacy of the treatment in relation to its adverse reactions. Scores on the EI range from 0 (marked improvement and no side-effects) to 16 (unchanged or worse, with side-effects outweighing therapeutic effects). Each component (subscales) of the CGI is rated separately; the instrument does not yield a global score.

**CDSS:** The CDSS has been specifically developed for the assessment of the level of depression in individuals with schizophrenia. It contains nine items. All ratings of the items are defined according to operational criteria from 0 to 3, where 0 indicates absence, 1 indicates mild, 2 indicates moderate and 3 indicates severe symptoms. The CDSS depression score is obtained by summing the scores of each item, with the final score ranging from 0 to 27.

**For efficacy:** Baseline evaluations of general and psychometric parameters of patients were conducted at the time of inclusion, followed by assessments at each visit at 2, 4, 6, 12, and 16 weeks. Scores from the aforementioned scales were noted at each follow-up visit, and improvements in scores, reflecting the efficacy of the administered drug were evaluated.

**For safety:** Treatment-emergent adverse events among schizophrenic patients treated with haloperidol, olanzapine, risperidone and aripiprazole were recorded. Adverse events monitoring was performed at every subsequent visit (excluding the initial visit). Adverse events were analysed based on the WHO-UMC Causality Assessment Scale [20].

**WHO-UMC causality Assessment Scale:** There are six causality categories for reported adverse events, ranging from unassessable/unclassifiable to certain, through conditional/unclassified, unlikely, possible and probable/likely. Each causality category has described assessment criteria to assist observers in choosing one category over another.

## STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical tool “GraphPad InStat” version 3.10 (trial version). A paired t-test was utilised for intra group comparisons at the following time points: 0 versus 2 weeks, 2 versus 4 weeks, 4 versus 6 weeks, 6 versus 12 weeks, 12 versus 16 weeks, and 0 versus 16 weeks. For intergroup comparisons between the four treatment groups, ANOVA was employed. A p-value of <0.05 was considered statistically significant, a p-value of <0.001 was regarded as highly significant, and a p-value of >0.05 was deemed non significant. For the inter group comparison of BPRS scores, the p-value was calculated using the online ANOVA tool available at <https://www.socscistatistics.com/tests/anova/default2.aspx>.

## RESULTS

The mean age of participants was 35.02±1.29 years. Most of the patients (n=72, 73.47%) were aged between 18 and 40 years. Of the participants, 60.20% (n=59) were male, and 39.80% (n=39)

Age group (years)	Gender	n (%)	Total
18-40	Male	44 (44.89)	72 (73.47)
	Female	28 (28.57)	
41-55	Male	10 (10.20)	17 (17.35)
	Female	7 (7.14)	
56-70	Male	5 (5.10)	9 (9.18)
	Female	4 (4.08)	

**[Table/Fig-2]:** Age-wise and gender-wise distribution of patients among study groups.

Drug group	Gender		Age (in years)	Education		Marital Status			Religion		
	Female	Male	Mean±SE	Literate	Illiterate	M	Um	D/S	Hindu	Muslim	Others
Haloperidol	10 (25.64)	14 (23.73)	39.63±3.52	21 (23.08)	3 (42.86)	15 (27.27)	8 (19.05)	1 (100)	17 (22.08)	4 (25)	3 (60)
Olanzapine	9 (23.08)	16 (27.12)	36.68±2.28	25 (27.47)	0	18 (32.73)	7 (16.67)	0	18 (23.38)	5 (31.25)	2 (40)
Risperidone	10 (25.64)	15 (25.42)	34.36±1.93	23 (25.27)	2 (28.57)	16 (29.09)	9 (21.43)	0	20 (25.97)	5 (31.25)	0
Aripiprazole	10 (25.64)	14 (23.73)	29.38±1.77	22 (24.18)	2 (28.57)	6 (10.91)	18 (42.86)	0	22 (28.57)	2 (12.5)	0
Total	39 (100)	59 (100)	35.02±1.29	91 (100)	7 (100)	55 (100)	42 (100)	1 (100)	77 (100)	16 (100)	5 (100)

**[Table/Fig-3]:** Demographic profile of schizophrenia patients in different study groups.

M: Married; Um: Unmarried; D/S: Divorced/Separated

Drugs	0 week	2 weeks	4 weeks	6 weeks	12 weeks	16 weeks
Haloperidol (n=24)	63.67±1.52	53.21±1.55*	45.58±1.65*	40.00±1.50*	35.33±1.36*	31.42±1.35*†
Olanzapine (n=25)	58.16±2.43	45.8±1.98*	36.8±1.73*	31.28±1.68*	25.36±1.08*	20.76±0.57*†
Risperidone (n=25)	61.44±3.82	48.64±2.95*	40.36±2.19*	33.08±1.74*	27.8±1.42*	24.52±1.19*†
Aripiprazole (n=24)	55.42±1.74	44.46±1.61*	38.13±1.23*	32.54±0.89*	27.67±0.80*	23.50±0.66*†
p-value (intergroup)	0.138425	0.026523	0.00442	0.000499	<0.00001	<0.00001

**[Table/Fig-4]:** Effect of different study drugs on changes in BPRS score (Mean±SEM) used to evaluate disease extent at 0, 2, 4, 6, 12 and 16 weeks.

\*: p<0.0001 versus last visit; †: p<0.0001 versus 0 week

were female [Table/Fig-2]. A majority of the patients (n=55, 56.12%) were married, while 42 (42.86%) were unmarried. Most patients identified as Hindus (n=77, 78.57%), followed by Muslims (n=16, 16.33%) and followers of other religions (n=5, 5.10%) [Table/Fig-3].

**Brief Psychiatric Rating Scale (BPRS):** Baseline BPRS scores across all groups were comparable (p>0.05). A significant reduction in BPRS scores was observed at each follow-up, with the Olanzapine group showing the most significant improvement at 16 weeks (mean BPRS score: 20.76±0.57, p-value <0.00001). Intergroup analysis revealed significant differences between Haloperidol and all atypical antipsychotics (p-value <0.001), as well as between Olanzapine and Risperidone (p-value <0.05) [Table/Fig-4].

**Positive and Negative Symptoms Scale (PANSS):** All groups exhibited a significant reduction in PANSS scores by the end of the study (p≤0.0001). Olanzapine achieved the greatest reduction (mean PANSS score: 33.72±0.60 at 16 weeks, p-value <0.001), followed by Risperidone [Table/Fig-5].

**CGI Subscale Analysis:** For Severity of Illness (SI) scores, significant improvements were observed in all groups, with atypical antipsychotics outperforming Haloperidol (p-value <0.001). For Global Improvement (GI) scores, differences emerged at 12 weeks, with Olanzapine and Risperidone showing significant improvements compared to Haloperidol (p-value <0.05). For the Efficacy Index (EI), Olanzapine demonstrated the highest efficacy, followed by Risperidone [Table/Fig-6].

**Calgary Depression Scale for Schizophrenia (CDSS):** Significant reductions in CDSS scores were recorded across all groups (p-value <0.001), with Olanzapine and Risperidone being more effective in managing co-morbid depression compared to Haloperidol [Table/Fig-7].

**Safety and Adverse Events:** For safety, treatment-emergent adverse events were documented in each study group, and causality assessments were performed using the WHO-UMC Causality Assessment Scale.

**Treatment-Emergent Adverse Events:** A total of 148 adverse events were recorded. The Haloperidol group reported the highest number of ADRs (n=57), followed by Risperidone (n=34) and Aripiprazole (n=30), while Olanzapine had the least frequency of ADRs (n=27). The difference between the ADR profiles of FGA and SGA was significant compared to the differences among the three SGAs. Common adverse events included dry mouth (43 events) and excessive appetite (28 events). The adverse events were mild and did not necessitate changes in dosing [Table/Fig-8].

**WHO-UMC Causality categories:** The ADRs were classified as



Drugs	0 week	2 weeks	4 weeks	6 weeks	12 weeks	16 weeks
Haloperidol	87.58±1.87	75.13±1.78*	64.71±1.92*	56.46±1.80*	48.79±1.52*	43.04±1.29* †
Olanzapine	85.2±3.58	69.76±3.00*	57.76±2.79*	48.56±2.46*	40.04±1.30*	33.72±0.60* †
Risperidone	85.88±3.61	70.28±3.14*	59.92±3.01*	49.36±2.55*	42.20±1.61*	37.40±1.07* †
Aripiprazole	86.25±2.88	71.38±2.54*	61.50±2.06*	51.50±1.61*	44.63±1.19*	38.04±0.93* †

**[Table/Fig-5]:** Effect of different study drugs on changes in PANSS score (Mean±SEM) used to evaluate disease extent at 0, 2, 4, 6, 12 and 16 weeks.

\*: p<0.0001 versus last visit; †: p<0.0001 versus 0 week

Time interval (in weeks)	Haloperidol	Olanzapine	Risperidone	Aripiprazole
<b>0 week</b>				
SI	5.25±0.11	5.08±0.16	5.04±0.17	4.75±0.12
GI	0±0	0±0	0±0	0±0
EI	0±0	0±0	0±0	0±0
<b>2 weeks</b>				
SI	4.83±0.14*	4.12±0.17*	4.20±0.20*	3.96±0.12*
GI	1.21±0.10	1.20±0.08	1.32±0.12	1.54±0.13
EI	2.29±0.20	1.04±0.04	1.80±0.32	1.08±0.08
<b>4 weeks</b>				
SI	4.29±0.14*	3.32±0.11*	3.72±0.17†	3.50±0.12†
GI	1.58±0.13	1.44±0.10	1.60±0.16	1.83±0.17
EI	2.79±0.40	1.96±0.31	2.16±0.44	2.13±0.36
<b>6 weeks</b>				
SI	3.58±0.15*	2.80±0.11†	3.08±0.14*	2.83±0.08*
GI	1.88±0.14	1.56±0.15	1.76 ±0.12	1.79±0.12
EI	2.38±0.46	2.52±0.43	2.68±0.39	3.46±0.42
<b>12 weeks</b>				
SI	3.04±0.14†	2.24±0.09*	2.56±0.11*	2.42±0.10†
GI	2.04±0.12	1.48±0.15	1.84±0.13	1.79±0.12
EI	3.04±0.42	2.28±0.41	3.04±0.41	3.88±0.47
<b>16 weeks</b>				
SI	2.67±0.11* §	2.04±0.07* §	2.16±0.09* §	2.04±0.04† §
GI	2.17±0.11	1.68±0.14	1.68±0.14	1.88±0.09
EI	4.50±0.27	2.20±0.42	2.84±0.46	3.54±0.43

**[Table/Fig-6]:** CGI subscale analysis.

\*: p<0.0001 versus last visit; †: p<0.001 versus last visit; ‡: p<0.05 versus last visit; §: p<0.0001 versus 0 week; SI: Severity index; GI: Global improvement; EI: Efficacy index

possible (66 events), probable (82 events), and certain (no events). In the FGA (Haloperidol) group, the maximum number of ADRs was reported during the initial two weeks of therapy. In the SGA groups, the maximum number of ADRs was reported between 4 and 6 weeks, with Risperidone contributing the most [Table/Fig-9].

## DISCUSSION

Schizophrenia is a complex psychiatric disorder characterised by a combination of positive symptoms (hallucinations, delusions), negative symptoms (emotional blunting, social withdrawal) and cognitive impairments, which significantly impact a patient's quality of life. Despite advancements in treatment, managing schizophrenia remains challenging, particularly due to variable responses to therapy and the adverse effect profiles of antipsychotic drugs.

This study demonstrated that Olanzapine was the most effective antipsychotic in improving psychometric scores, as evidenced by significant reductions in BPRS and PANSS scores. These findings align with recent meta-analysis, which confirm Olanzapine's superior efficacy in treating both positive and negative symptoms compared to conventional antipsychotics and certain atypical agents, such as Aripiprazole [21,22]. Moreover, Risperidone was found to be equally effective in improving PANSS and CDSS scores, highlighting its dual efficacy in managing both psychotic and depressive symptoms [23], particularly in the context of suicide being a leading cause of mortality in psychosis [4].

Aripiprazole, while effective, showed slightly lower efficacy in improving PANSS scores compared to Olanzapine and Risperidone. This observation was consistent with previous studies suggesting that Aripiprazole may be less effective in addressing severe negative symptoms, but it offers advantages in terms of tolerability and metabolic profile [11,24]. Haloperidol, as a typical antipsychotic,

Drug group	0 week	2 weeks	4 weeks	6 weeks	12 weeks	16 weeks
Haloperidol	10.79±0.33	9.04±0.43*	7.92±0.40*	6.92±0.44†	5.33±0.42*	4.46±0.36* §
Olanzapine	9.64±0.92	6.80±0.71*	4.96±0.54*	4.04±0.56†	2.96±0.45†	1.96±0.39‡ §
Risperidone	10.2±0.91	8.16±0.80*	6.48±0.75*	5.16±0.75*	3.64±0.54†	2.52±0.38* §
Aripiprazole	10.17±0.98	8.13±0.88*	6.67±0.77*	5.50±0.68†	4.25±0.64*	3.58±0.61† §

**[Table/Fig-7]:** Effect of different study drugs on changes in CDSS score (Mean±SEM) used to evaluate disease extent at 0, 2, 4, 6, 12 and 16 weeks

\*: p<0.0001 versus last visit; †: p<0.001 versus last visit; ‡: p<0.05 versus last visit; §: p<0.0001 versus 0 week

Adverse events	Haloperidol (n=24)	Olanzapine (n=25)	Risperidone (n=25)	Aripiprazole (n=24)	Total
Excessive appetite	15 (62.5%)	4 (16%)	5 (20%)	4 (16.67%)	28
Dry mouth	20 (83.33%)	11 (44%)	5 (20%)	7 (29.17%)	43
Difficulty falling asleep	-	-	1 (4%)	-	1
Drowsiness	12 (50%)	2 (8%)	2 (8%)	3 (12.5%)	19
Increased sleep	2 (8.33%)	5 (20%)	4 (16%)	2 (8.33%)	13
Decreased appetite	-	-	1 (4%)	10 (41.7%)	11
Heaviness in extremities	-	-	1 (4%)	1 (4.17%)	2
Hot flushes	-	-	1 (4%)	1 (4.17%)	2
Tremors	-	-	1 (4%)	-	1
Dry skin	3 (12.5%)	-	3 (12%)	-	6
Dizziness	-	1 (4%)	1 (4%)	-	2
Fatigue	-	-	-	1 (4.17%)	1
Headache	-	3 (12%)	1 (4%)	-	4

Menstrual disturbances	4 (16.67%)	-	3 (12%)	1 (4.17%)	8
Hypersensitivity (rashes)	-	-	1 (4%)	-	1
Constipation	1 (4.17%)	1 (4%)	4 (16%)	-	6
Total	57	27	34	30	148

[Table/Fig-8]: Treatment-emergent adverse events.

Visit on	Type of ADR	Haloperidol (n=24)	Olanzapine (n=25)	Risperidone (n=25)	Aripiprazole (n=24)	Total
2 weeks	Possible	21 (87.5%)	0	0	0	21
	Probable	7 (29.17%)	2 (8%)	0	3 (12.5%)	12
	Certain	0	0	0	0	0
4 weeks	Possible	9 (37.5%)	3 (12%)	4 (16%)	1 (4.17%)	17
	Probable	13 (54.17%)	4 (16%)	2 (8%)	2 (8.33%)	21
	Certain	0	0	0	0	0
6 weeks	Possible	1 (4.17%)	2 (8%)	8 (32%)	7 (29.17%)	18
	Probable	5 (20.83%)	9 (36%)	13 (52%)	4 (16.67%)	31
	Certain	0	0	0	0	0
12 weeks	Possible	0	1 (4%)	4 (16%)	2 (8.33%)	7
	Probable	1 (4.17%)	4 (16%)	2 (8%)	2 (8.33%)	9
	Certain	0	0	0	0	0
16 weeks	Possible	0	2 (8%)	0	1 (4.17%)	3
	Probable	0	0	1 (4%)	8 (33.33%)	9
	Certain	0	0	0	0	0
Total	Possible	31	8	16	11	66
	Probable	26	19	18	19	82
	Certain	0	0	0	0	0
G. Total		57	27	34	30	148

[Table/Fig-9]: ADRs observed: WHO-UMC causality categories.

demonstrated efficacy in controlling positive symptoms; however, it lagged behind atypical agents in improving negative and cognitive symptoms, corroborating earlier reports [25].

All treatment groups were comparable regarding baseline disease severity (CGI-SI). The changes in CGI-SI and CGI-GI scores were maximal with Olanzapine in the present study, which correlates with earlier findings [26]. Additionally, Risperidone showed a significant reduction at 2, 4, 6, 12, and 16 weeks compared to the baseline scores [27,28]. In the CGI-EI, Olanzapine demonstrated maximum efficacy, followed by Risperidone, both of which were superior to the conventional antipsychotic Haloperidol. These findings support earlier reports from meta-analysis of various comparative studies suggesting that newer agents are equivalent to or may exceed the efficacy of conventional antipsychotics [29]. However, there was no remarkable difference in the decrease in CGI-SI or CGI-GI between Aripiprazole and Haloperidol, as observed in previous studies [30].

Adverse effects are a major determinant of treatment adherence. As expected, Haloperidol was associated with a higher incidence of EPS, including tremors and rigidity, compared to atypical antipsychotics. These findings are consistent with the dopamine D2 receptor blockade in the basal ganglia, which is a hallmark of typical antipsychotic pharmacodynamics [25].

While effective, Olanzapine and Risperidone were associated with weight gain and increased appetite, findings that are supported by broader literature [31,32]. Conversely, Aripiprazole exhibited the least metabolic disturbances, making it a preferable choice for patients at risk of metabolic syndrome [33].

However, the lower incidence of weight gain must be balanced against its relatively modest efficacy in severe cases [11].

Olanzapine is regarded as a first-line therapy due to its robust efficacy, demonstrating superior improvements in BPRS, PANSS, and CGI scores, particularly for both positive and negative symptoms, making it ideal for patients requiring comprehensive

symptom control. Risperidone is a strong candidate in terms of efficacy, making it a practical choice where psychosis is associated with depression. Aripiprazole offers a safer profile with minimal compromise on efficacy in severe cases, minimising metabolic disturbances and making it a favourable choice for metabolically vulnerable patients.

Haloperidol remains a viable option for managing acute psychosis in specific scenarios; however, it is less suited for long-term maintenance therapy due to its adverse effect profile, particularly EPSs, and a lack of efficacy in addressing negative and cognitive symptoms. Thus, while Haloperidol is effective for acute symptom control, it may be best reserved for cases where atypical antipsychotics are contraindicated or unavailable.

### Limitation(s)

The study's open-label design and relatively small sample size (n=98) could introduce bias and limit generalisability. Additionally, the study duration of 16 weeks may not adequately capture the long-term effects of antipsychotics, particularly their metabolic and neurological impacts. Future studies with larger cohorts, longer follow-ups, and double-blind designs are warranted.

### CONCLUSION(S)

The study reaffirms the pivotal role of atypical antipsychotics in improving treatment outcomes for schizophrenia, marking a significant step forward in the quest for individualised, patient-centred care by highlighting their ability to enhance therapeutic outcomes, reduce relapse rates and improve patient compliance. By addressing the limitations of conventional agents, these newer drugs have significantly expanded the therapeutic horizon, offering patients a better chance of functional recovery and, consequently, an improved quality of life. By bridging efficacy and safety, these findings provide a roadmap for optimising schizophrenia therapy and improving the lives of millions affected by this debilitating disorder.

Larger, double-blind studies with extended follow-up periods are needed to evaluate the long-term safety and efficacy of these antipsychotics. Research focusing on personalised medicine, incorporating genetic and biomarker-driven approaches, could further refine treatment strategies. Moreover, addressing the metabolic side-effects of atypical antipsychotics remains a critical area for future innovation.

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