ORIGINAL ARTICLE

Effect of Antipsychotic on the Dimension of Auditory Hallucination Among Patients with Schizophrenia

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ABSTRACT

INTRODUCTION: Auditory hallucination (AH) is the most common type of hallucinations in individuals with schizophrenia. Assessing the multidimensional aspects of AH provides more precise insights, particularly regarding associated psychological sequelae. This study aimed to examine the short-term effects of antipsychotics treatment on the emotional, cognitive and physical dimension of AH. **MATERIALS AND METHODS:** A total of 74 patients with schizophrenia with relapsing episodes were recruited. The Psychotic Symptoms Rating Scale subscale Auditory Hallucination. (PSYRATS-AH) was administered at baseline, and after 2 weeks and 4 weeks of treatment. Patients were treated with atypical, typical, or a combination of both types of antipsychotics. The emotional, cognitive and physical components of PSYRATS-AH were analysed. **RESULTS:** Most participants were Malay (89.2%), single (63.5%), unemployed (70%), and on atypical antipsychotic treatment (71.6%). At 4 weeks, there was a significant reduction in overall AH scores compared to baseline. Both atypical and combination antipsychotic regimen showed a significant difference in all three components, namely emotional ($\chi2=43.9$, $p<0.05$ and $\chi2=27.8$, $p<0.05$), cognitive ($\chi2=34.1$, $p<0.05$ and $\chi2=19.0$, $p<0.05$), and physical ($\chi2=39.5$, $p<0.05$ and $\chi2=30.5$, $p<0.05$). However, those on typical antipsychotic showed a poorer response in the physical component ($\chi2=5.4$, $p>0.05$). **CONCLUSION:** Atypical and combination antipsychotic regimen demonstrated greater effectiveness in improving the emotional, cognitive, and physical dimension of AH. Typical antipsychotics alone were less effective, particularly in addressing physical symptoms. These findings support the preferential use of atypical antipsychotics managing the multidimensional aspects of AH in schizophrenia.

Keywords
auditory hallucination, PSYRATS, antipsychotic, schizophrenia

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INTRODUCTION

Auditory hallucination (AH) is a prominent symptom of schizophrenia, accounting for 60% to 80% of all hallucinations.[1] Various theoretical models such as cognitive neurobiology, psychopathology, neuroimaging, and dimensional frameworks have been proposed to explain their occurencee.[2] These hallucinations are dimensional in nature, conceptualized through cognitive, perceptual, and emotional domains.[3] The cognitive dimension involves an inability to control voices, the perceptual dimension refers to voices perceived as external; and the emotional dimension includes voices with a negative or derogatory tone. This emotional aspect often causes significant distress and is associated with depressive symptoms.[4]

Clinical evaluation of AHs is complex due to factors such as number of voices, their perceived origin, interactivity, and mood congruence. A thorough assessment of their content and context is crucial, as these symptoms significantly influence treatment decisions. Considerations typically include psychosocial background, patient's preferences, treatment costs, and tolerability. A multidimensional approach allows for more tailored treatment strategies. For example, a study applying this framework prior to mindfulness therapy demonstrated improved voice control and reduced distress at 12 weeks.[5]

Treatment efficacy is often measured using the Positive and Negative Syndrome Scale (PANSS), which is regarded

as the gold standard.[5-7] However, PANSS provides only a general overview and does not address specific features of hallucination.[8] In contrast, the Psychotic Symptoms Rating Scale (PSYRATS) evaluates eleven dimensions of AHs, grouped into emotional, cognitive, and physical categories.[9,10] PSYRATS is widely used to assess the effectiveness of psychological interventions.[5,11]

Although the pharmacological treatment of schizophrenia is well researched, there is limited focus on antipsychotic effects on individual hallucination dimensions. Some studies have used PSYRATS to evaluate delusional dimensions.[12] A six-month trial reported early improvements in distress and loudness, supporting the observation that hallucinations respond to treatment sooner than delusions.[13] This further validates PSYRATS as a reliable tool for symptom-specific evaluation.

Given the limited data on the pharmacological effects on AH dimensions, this study aimed to fill that gap by investigating the short-term impact of typical, atypical, and a combination of both antipsychotics on AH dimensions in schizophrenia. The findings are expected to support the integration of dimensional assessments into treatment planning, complementing traditional measures of efficacy and tolerability. Additionally, this research will contribute valuable local data to inform future outcome studies on schizophrenia.

MATERIALS AND METHODS

This prospective observational cohort study involved 74 patients with schizophrenia with relapsing episodes, recruited through simple random sampling from the psychiatric unit of a tertiary care and referral hospital in Peninsular Malaysia. Eligible participants met DSM-5 criteria for schizophrenia, were aged 18 to 65, Malay-speaking, and free from severe medical conditions (e.g., CNS infection, cerebrovascular disease, head trauma). All participants had Brief Psychotic Rating Scale (BPRS) scores below 52 and presented with relapse symptoms, primarily AHs.[4] Relapse was defined as at least one acute psychotic episode lasting seven days or more.[14]

The study was conducted between June and November 2019 in compliance with institutional and national ethical guidelines and regulations. Ethical approval was obtained from both institutional and national research ethics committees (FF-2019-206; NMRR-18-2548-42942). Written informed consent was obtained at the baseline visit from both patients and their caregivers once the patients were clinically assessed to have the capacity to understand and comprehend the nature and purpose of the study. Consent was only taken when participants were mentally stable and were able to engage in meaningful discussion.

Assessments were conducted at three time points: baseline (over three sessions), week 2, and week 4. This timeline aligns with recommendations by the British Association of Psychopharmacology and the National Institute for Health and Care Excellence (NICE) suggest a four to six weeks period for evaluating antipsychotic efficacy. Throughout the study, symptom severity, side effects, and patient well-being were closely monitored. All participants were managed by their treating psychiatrists according to standard clinical protocols, while AHs were directly assessed by the authorS.

Instruments

A sociodemographic questionnaire was used to collect information on age, gender, marital status, education level, employment status, duration of illness, and type of medication prescribed. Symptom severity was measured using the 18-item Brief Psychiatric Rating Scale (BPRS), a clinician-administered tool. Only patients with BPRS scores below 52 were included in the study. Patients with score of 52 and higher were excluded to avoid potential confounding effects from severe illness.[4]

Auditory hallucination (AH) dimensions were assessed using the Malay version of the Psychotic Symptom Rating Scales – Auditory Hallucinations subscale (MyPSYRATS-AH),[15] a validated semi-structured interviewer-rated tool comprising of 11 items. These items evaluated key features over the past week, including frequency, duration, location, loudness, perceived voice origin, negative content (amount and degree), distress (amount and intensity), degree of disruption to life, and controllability.

Each item was rated on a scale from 0 to 4, with higher scores indicating greater severity. The items are grouped into three subscales: emotional (negative content, distress), cognitive interpretation (origin, disruption, controllability), and physical characteristics (loudness, frequency, duration, location).[16] MyPSYRATS-AH has demonstrated strong validity and reliability within the local population and shows minimal socio-cultural bias.[15]

Statistical analysis

Statistical analyses were performed using SPSS version 25. Descriptive statistics were used to summarize the sociodemographic and clinical characteristic of respondents. Means and standard deviation (SD) were reported for continuous variables (e.g., age, PSYRATS scores), while frequencies and percentages were used for categorical variables.

Normally distributed data were analyzed using independent sample t-tests and one-way ANOVA. For non-normally distributed data, Mann-Whitney U and Kruskal-Wallis tests were employed. Friedman's test was used to assess changes in PSYRATS-AH scores across the treatment period and between different antipsychotic groups

RESULTS

Sociodemographic and clinical characteristics

A total of 74 respondents completed the four-week assessment. Table I presents the sociodemographic data of the respondents. The mean age was 38.53 (SD=11.4), with 54% being male. Majority of respondents were Malay (89.2%), single (63.5%), unemployed (70%) and all (100%) belonged to the low-income group (B40, with household income less than RM 3,000). Across the study, the mean PSYRATS-AH scores for male respondents were consistently lower than those for female, but this difference was not statistically significant at both baseline ($p=0.72$) and week 4 ($p=0.6$). A significant improvement in PSYRATS-AH scores over time was observed among single respondents ($p<0.05$). However, the improvements among married and divorced respondents were not statistically significant ($p>0.05$).

Table I: Sociodemographic and clinical characteristic dimension of AH according PSYRAT-AH score (n=74)

Variables	Number (n)	Frequency (n)	Mean (SD)	PSYRAT-AH Score		
				Baseline (mean, SD)	Week 2 (median, IQR)	Week 4 (median, IQR)
Age			38.53 (11.4)			
Gender						
Male	40	54.1		26.6	15.5	7.00
Female	34	45.9		(6.93)	(24)	(20)
Marital Status						
Single	47	63.5		28.9	18.0	2.0
Married	19	25.7		(6.8)	(23)	(20)
Divorced	8	10.8		28.3	23.0	13.0
Race						
Malay	66	89.2		28.6	18.0	8.5
Chinese	5	6.8		(7.2)	(24)	(22)
Indian	2	2.7		30.8	21.0	1.0
Aborigine	1	1.4		(5.6)	(10)	(10)
Education Level	14	18.9		27.8	17.0	18.0
Primary school	49	66.2		(6.9)	(30)	(25)
Secondary	11	14.9		28.8	18.0	1.0
Employment Status						
Employment	22	30		28.6	19.0	8.0
Unemployed	52	70		(7.2)	(24)	(22)
Salary						
B40	74	100				
M40						
Duration of Illness			11.11 (9.6)			

Antipsychotic Treatment

Antipsychotics used in this study included typical antipsychotics (Haloperidol, Perphenazine, Trifluoperazine, Zuclopenthixol decanoate, Flupenthixol decanoate) and atypical antipsychotics (Risperidone, Olanzapine, Quetiapine, Aripiprazole, Paliperidone, Clozapine, and Amisulpiride). Some respondents received a combination of both typical and atypical agents. At baseline, the majority of the respondents were prescribed atypical antipsychotics alone (71.6%), followed by combination therapy (16.2%) and typical antipsychotics alone (12%). By week 2, nine respondents (12%) had been switched to a different medication group, mainly to enhance treatment response by introducing an additional route of administration. Only one respondent (1.35%) was switched from a typical to an atypical antipsychotic due to extrapyramidal side effects. The medication switches involved several strategies, including transitions from atypical to combination therapy, atypical to typical, typical to combination, and typical to atypical antipsychotics. Following these changes, the newly assigned treatment group was maintained until week 4. The most common switch was from atypical to the combination therapy (n=6).

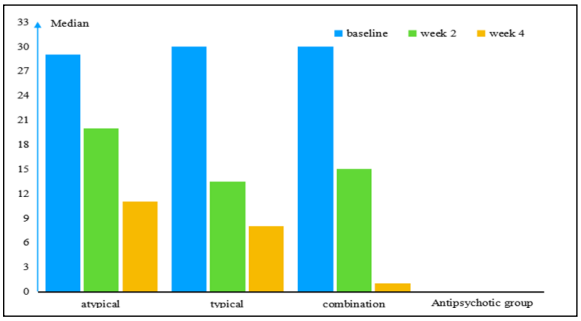

Figure 1: Total PSYRATS score (median) for 3 groups of antipsychotics over 4 weeks

The Effect of Different Antipsychotic Groups on AH Dimensions Based on PSYRATS-AH Scores

PSYRATS-AH scores were recorded at baseline, week 2, and week 4 of assessment. Overall, there was a statistically significant difference in PSYRATS-AH score from baseline to week 4 ($p<0.001$). While this indicates general improvement, further analysis was conducted to determine whether any specific group of antipsychotics was superior to other antipsychotics at a certain time of treatment. Thus, separate comparisons were made at weeks 2 and 4 to evaluate the effects of all the three antipsychotic groups to the PSYRATS score. At week 2, there was no statistically significant difference in PSYRATS-AH scores among the three treatment groups, with a median score of 18 (IQR=24), $p=0.066$. Similarly, at week 4, the differences remained statistically non-significant, with a median score of 8 (IQR=22), p=0.235T.

Further analysis was performed within each treatment group to assess the magnitude of change in PSYRATS-AH scores over time. For the atypical antipsychotics group, a significant reduction was observed from baseline (median=29, IQR=9) to week 2 (median=20, IQR=25) and further to week 4 (median=11, IQR=23), with $p<0.001$. Similarly, for the typical antipsychotic group, scores decreased from baseline to week 2 (median=13.5, IQR=18) and week 4 (median=8, IQR=28.75), showing a statistically significant improvement ($p=0.023$). The combination therapy group also demonstrated a significant reduction in scores over four weeks, from 30 (IQR=13) to 15 (IQR=23), and further to 1 (IQR=16), with $p<0.001$ (Figure 1).

Table II presents improvements across all eleven dimensions of AHs from baseline to week 4 in patients treated with atypical antipsychotics and combination therapy (all $p<0.05$). These improvements include perceptual dimensions (e.g., frequency, location, loudness) and emotional-cognitive dimensions (e.g., negative content, distress, disruption, controllability). In contrast, the typical antipsychotic group showed significant improvements only in select dimensions, primarily related to emotional and cognitive aspects. No significant changes were observed in the frequency, location, loudness, and controllability dimensions ($p>0.05$), suggesting a more limited impact on the full spectrum of AH symptoms.

Table II: Effect of atypical, typical and combination antipsychotics on the dimensions of AH

	Statistical test, p value		
AH (dimension)	**Atypical antipsychotic (n=47)**	**Typical antipsychotic (n=8)**	**Combination (n=19)**
Frequency	$\chi2$ =38.70, p< 0.001**	$\chi2$=3.85 p=0.146	$\chi2$=29.10 p< 0.001**
Duration	$\chi2$ =51.25, p< 0.001**	$\chi2$=11.40 p=0.003**	$\chi2$=31.46 p< 0.001**
Location	$\chi2$ =7.83, p= 0.02**	$\chi2$=2.00 p=0.368	$\chi2$=14.77 p< 0.001**
Loudness	$\chi2$ =22.96, p< 0.001**	$\chi2$=0.43 p=0.807	$\chi2$=21.96 p< 0.001**
Origin of voice	$\chi2$ =26.25, p< 0.001**	$\chi2$=6.28 p=0.043**	$\chi2$=21.03 p< 0.001**
Amount of negative content	$\chi2$ =39.56, p< 0.001**	$\chi2$=9.41 p=0.009**	$\chi2$=24.11 p< 0.001**
Degree of negative content	$\chi2$ =27.11, p< 0.001**	$\chi2$=7.47 p=0.024 **	$\chi2$=22.75 p< 0.001**
Amount of distress	$\chi2$ =39.84, p< 0.001**	$\chi2$=7.72 p=0.021**	$\chi2$=24.97 p< 0.001**
Intensity of distress	$\chi2$ =40.28, p< 0.001**	$\chi2$=10.41 p=0.005**	$\chi2$=24.04 p< 0.001**
Disruption to life	$\chi2$ =37.71, p< 0.001**	$\chi2$=8.87 p=0.012 **	$\chi2$=18.25 p< 0.001**
Controllability	$\chi2$ =29.64, p< 0.001**	$\chi2$=5.10 p=0.078	$\chi2$=15.50 p< 0.001**

*friedman test, p-value < 0.05**

The effect of antipsychotic treatment on the three main components of AH.

Figure 2 and 3 illustrate the effects of atypical and typical antipsychotics, respectively on the three main components (subscale) of AHs as defined by the PSYRATS-AH. These components were emotional, cognitive and physical. The emotional consisted of the amount and degree of negative content, and the amount and intensity of distress. The cognitive component consisted of perceived origin of the voice, disruption to daily life, and controllability.

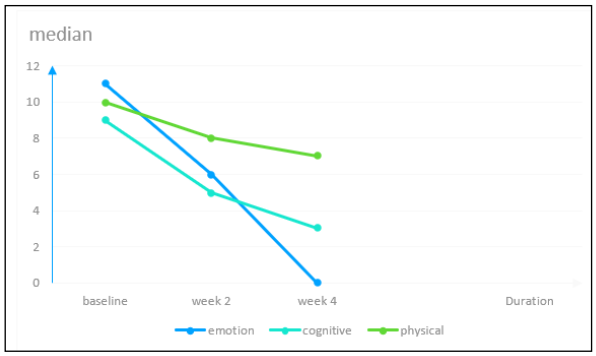

Figure 2: Effect of atypical antipsychotic on PSYRATS components

The physical component consisted of frequency, duration, location, and loudness of the voices. All antipsychotic groups (Figure 2, 3 and 4) demonstrated a significant reduction across all three components of AH, with the exception of the physical components in the typical antipsychotic (Figure 3). In this group, the reduction in the physical symptoms did not reach statistical significance (χ=5.448, p =0.066).

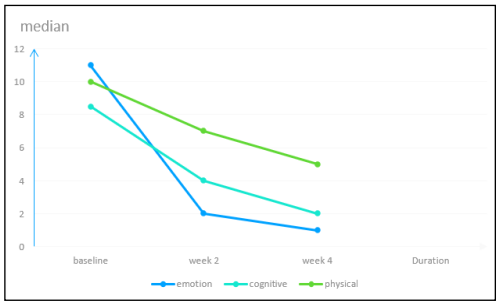

Figure 3: Effect of typical antipsychotic on PSYRATS components

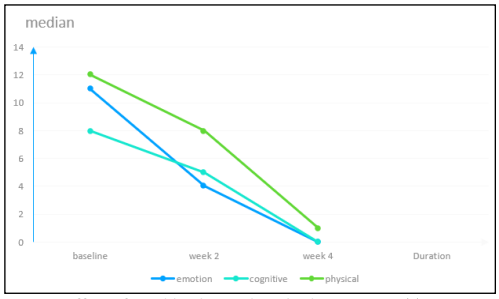

Figure 4: Effect of combination antipsychotic on PSYRATS components

DISCUSSION

This study investigated the short-term effects of antipsychotics on the dimensions of AHs in patients with relapsed schizophrenia. Antipsychotics were categorized into three groups: atypical, typical and combination therapy, with assessments conducted at weeks 2 and 4.[17,18] The validated Malaysian version of the PSYRATS-AH[16] scale was used for its ability to provide a detailed assessment of AH dimensions.

A total of 74 patients completed the study, with Malays comprising the majority (89.2%). This proportion is higher, though generally consistent with previous findings with one study reporting 66.2% Malay representation among patients with schizophrenia.[18] Notably, another study on AH dimensions reported less Malay population representation at 36.7% which could possibly be due to regional differences and patterns of psychiatric service utilization.[4] Local clinical data indicate that Malay patients account for approximately 66%-73% of psychiatric unit visits, which may explain the higher representation observed in this study.

In this study, 71.6% of patients were treated with atypical antipsychotics, consistent with a retrospective analysis reporting that atypical antipsychotics accounted for 79.9% of all prescriptions to treat schizophrenia, with a steady increase in prescriptions times.[19] The emergence of atypical antipsychotics, known for their superior efficacy in alleviating schizophrenia symptoms,[20] has led some clinicians to prefer them over typical antipsychotics. Atypical antipsychotics are also associated with fewer extrapyramidal side effects and improved cognitive function, making them a preferred option in clinical practice. [21]

Pharmacological treatment remains a cornerstone in managing schizophrenia, as evidenced by the improvements in AH scores observed in this study. However, no significant differences were found in AH dimension scores between the different antipsychotic types at both week 2 and week 4 week. These findings align with those from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and subsequent meta-analyses, which found no substantial difference in overall efficacy between atypical and typical antipsychotics in treating schizophrenia.[22] Although direct comparisons with the CATIE trial are limited due to differences in study design, both studies reported minimal differences in efficacy between the two antipsychotic classes during the observed periods.

One potential contributing factor to these findings may be genetic polymorphisms affecting antipsychotic drug metabolism, particularly those involving cytochrome P450 (CYP) enzymes.[23] Research indicates that Asian populations, including Malaysians, exhibit distinct CYP2D6 and CYP3A5 polymorphisms compared to Western populations. For instance, the CYP2D6*10 allele, which reduces enzyme activity, is prevalent in up to 50% of certain East Asian populations.[24] These genetic variations may influence the pharmacokinetics of antipsychotics, affecting therapeutic efficacy and side effect profiles.

While all antipsychotic groups showed overall

improvement in AHs, this study found that typical antipsychotics had a comparatively limited effect on the physical characteristic dimensions of AH, particularly frequency, loudness, and duration. It is hypothesized that each dimension of AH may respond differently to pharmacological treatment.[25] One possible explanation for this finding is the small sample size of patients receiving typical antipsychotics, which may have limited the pwer to detect significant changes compared to the atypical and combination groups.

Atypical antipsychotics exert their effects primarily through dopamine D_2 receptor antagonism in the mesolimbic pathway, reducing positive symptoms such as hallucinations. Additionally, their antagonism of serotonin (5-HT2A) receptors enhances dopaminergic activity in the mesocortical pathway, potentially improving cognitive deficits[26] and negative symptoms.[26] Structural neuroimaging studies have implicated cortical thinning in the left middle temporal gyrus and disrupted connectivity between the right middle frontal gyrus and the left superior temporal gyrus in the pathophysiology of AH.[27,28] The dorsal striatum, which receives input from speech-processing areas, is also thought to contribute to the misperception of internal thoughts as external voices.[29] Hyperactivity within the mesolimbic system further underpins the neurobiological basis of AH.[30]

By modulating these neural circuits and neurotransmitter systems, atypical antipsychotics may influence both structural and functional brain changes. Evidence suggests that early treatment response may help restore disrupted connectivity, correlating with reductions in AH severity. This aligns with our study findings, where atypical antipsychotics produced broader improvements across all AH dimensions. These results are consistent with a 2016 study that had used the PSYRATS scale and reported similar outcomes.[31] The same study also reported that similar to atypical agents, drugs with lower D2 receptor affinity showed enhanced efficacy when combined with transcranial direct current stimulation.

Recent studies further support that typical antipsychotics, which primarily antagonize dopamine D2 receptors, may be less effective in alleviating AH due to their limited modulation of other neurotransmitter systems. In contrast, atypical antipsychotics with dual dopamine and serotonin antagonism, shows better therapeutic profile for AH.[26] A pragmatic randomized controlled trial comparing the efficacy of olanzapine, amisulpride, and aripiprazole in reduction of AH further supports this superiority among of certain atypical antipsychotics.[32]

A small subset of participants underwent medication changes prior to the week 2 assessment, mainly involving the addition of depot typical antipsychotics to address adherence concerns. However, due to the limited number of cases, further subgroup analysis was not performed. Medication non-adherence remains a persistent challenge in the treatment of schizophrenia, with approximately 50% of patients demonstrating poor adherence.[33-34] This limitation highlights the need to incorporate adherence monitoring in future studies, especially those with a longer follow-up period.

The short-term nature of this study presents a notable limitation, as it may not fully capture the longitudinal effects of antipsychotic treatment on AH. Moreover, there are limited research exploring the multidimensional aspects of AH using PSYRATS, thus making direct comparisons with existing literature challenging. Some studies have employed the PANSS for outcome assessment, which lacks the dimensional specificity provided by the PSYRATS.[35] Hence, the current findings may aid in the detailed evaluation of AH dimensions offered by PSYRATS and further enabling clinicians to tailor treatment based on specific symptom dimensions. For example, interventions such as cognitive behavioral therapy (CBT) and metacognitive training have shown efficacy in addressing distress-related dimension of AHs[36-37] Therefore, the current study findings may aid clinicians in refining pharmacological strategies and integrating psychological therapies, while also taking into account tolerability and side effect profiles.

Future research should further explore the comparative effectiveness of pharmacological and psychological interventions across different AH dimensions. The present study provides preliminary evidence that may

serve as a catalyst for larger, long-term investigations in this area.

This study has several limitations. As an observational study design, treatment decisions including antipsychotic choice and dosage were based on clinical judgment, introducing selection bias and confounding by indication, particularly for patients with more severe symptoms. Variability in dosing and medication switching further complicate the interpretation of results. Without randomization or a standardized protocol, attributing outcomes solely to medication type is challenging.

The small sample size and short observation period limit the study's statistical power and its ability to draw long-term conclusions. The absence of a control group restricts causal inferences. Furthermore, factors such as medication adherence, polypharmacy, psychosocial variables, and comorbidities were not evaluated, despite their known impact on treatment outcomes.

Additionally, the study had only included patients who had episodes of schizophrenia relapses from a single district limiting generalizability to newly diagnosed patients or broader populations. Future research should employ randomized controlled, multicenter designs with larger samples and longer follow-up. In smaller populations, purposive sampling may offer a more efficient approach.

Despite these limitations, this study's strength lies in the standardized assessments conducted across three time points by a single rater, minimizing inter-rater variability. The findings provide early insights that may assist clinical decision-making in managing schizophrenia.

CONCLUSION AND RECOMMENDATION

This study underscores the importance of addressing the multidimensional nature of auditory hallucinations in schizophrenia to inform targeted treatment strategies. While all antipsychotic groups demonstrated short-term improvements, typical antipsychotics appeared less effective in alleviating the physical characteristics of hallucinations. Atypical antipsychotics, either alone or in combination, showed greater overall efficacy and may be preferred in clinical decision-making alongside psychosocial interventions.

However, limitations such as a small sample size, short observation period, and the absence of a control group warrant caution in interpreting these findings. Thus, future research should emphasize larger, multicenter randomized controlled trials with extended follow-up periods and adherence monitoring. Additionally, evaluating the utility of PSYRATS in routine clinical settings may enhance its applicability and support more nuanced, dimension-specific treatment approaches.

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CONFLICT OF INTEREST

None

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