

Homocysteine Levels and Clinical Outcomes in Schizophrenia—A Pilot Randomized Controlled Trial

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Abstract

Objectives: To find out the relation between homocysteine levels in peripheral blood and the effectiveness as well as the safety of haloperidol and olanzapine in schizophrenia treatment.

Materials and Methods: A prospective randomized parallel-group open-label interventional clinical trial was conducted on 40 mild to moderate schizophrenia patients. To compare the efficacy of olanzapine and haloperidol Brief Psychiatric Rating Scale (BPRS) score was used. Homocysteine levels of peripheral blood and Abnormal Involuntary Movement Scale scores were evaluated.

Results: BPRS score improved in both groups on day 14 and day 28. But significantly more with olanzapine (P value = .001). The olanzapine group showed a higher reduction (13.91 ± 0.47 to 9.74 ± 0.5) in homocysteine levels than the haloperidol group. Also, the BPRS scores negatively correlated ($r = -0.66$) to homocysteine levels.

Conclusion: Therefore, our study shows that peripheral blood homocysteine levels can be used to predict and assess the treatment outcome in schizophrenia patients. Biomarker driven approach in schizophrenia will allow the patients to be treated promptly with the right drug. In this light, personalized treatment holds great potential in the future.

Keywords

Olanzapine, haloperidol, homocysteine, RCT, therapeutic biomarker, correlation study

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Introduction

Schizophrenia is one of the 15 leading causes of disability worldwide¹ and is a major contributor to the global burden of diseases. Schizophrenia is projected as the eighth leading cause of Disease Adjusted Life Years worldwide in the age group 15–44 years. Globally, 23 million people suffer from schizophrenia, and between 1990 and 2016, the prevalence increased from 13.1 million to 20.9 million cases.² In India, the prevalence of schizophrenia is 3/1000 individuals.^{3,4} Schizophrenia affects more men (12 million) than women (9 million).^{5–8} Incidence of schizophrenia is higher in men, especially in late teenage, but declines in middle age, whereas in females, the incidence is high in adolescence and low in middle age.⁹ Schizophrenia patients are often associated with

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cardiovascular diseases, metabolic disease, and infection, leading to a 2–3 times more chance of death than the general population. Moreover, it is also associated with a high rate of recurrence (90%) and chronicity.¹⁰ Schizophrenia, as a clinical syndrome of disruptive psychopathology, involves cognition, perception, emotion, and other aspects of behavior.¹¹ Schizophrenia is linked to significant disability over the world, and it can affect academic, professional, as well as social well-being. It is also linked to an increased risk of suicidal behavior. Suicide has become the second largest factor of death in people aged 15–29,¹² and 10.1% of suicides were in confirmed cases of schizophrenia.¹³ The suicide incidence in schizophrenic adults was 6.8/1000 population/year. The relative risk of suicide in schizophrenia cases to others was 23.8.¹⁴

There are known and effective treatments for schizophrenia, but the majority of chronic schizophrenic patients lack access to treatment. Globally, the median treatment gap for schizophrenia is 32.2%,¹⁵ According to the World Health Organization (WHO) and the National Mental Health Survey, the treatment gap for mental disorders in developing countries is 76%–85% and 83%, respectively.¹⁶ Indian mental health care has a significant treatment disparity, which may be due to social stigma, cultural beliefs, and financial limitations.

Schizophrenia patients are treated with typical and atypical antipsychotic drugs. Atypical drugs are most commonly preferred nowadays to overcome extrapyramidal side effects of typical antipsychotic drugs. The dopamine theory postulates that schizophrenia might be caused by increased dopaminergic neurotransmission. Antipsychotic drugs act by targeting dopamine receptors. However, the antipsychotic effects are not seen until 2–4 weeks of treatment. Chlorpromazine was the first antipsychotic drug introduced in 1952, followed by other antipsychotic drugs, which revolutionized the treatment for schizophrenia with limited side effects. Response to antipsychotic treatment showed variations between patients. Up to 30% of schizophrenia patients do not respond adequately to antipsychotic drugs. This inter-individual response to antipsychotic treatment has led to several studies to find biological markers and also aims at establishing a relation with therapeutic response.

A biomarker is a measure of normal physiological, biochemical, pathological events, and pharmacological effects on a potential treatment that is objectively tested and assessed.¹⁷ Biomarker-based therapeutics play a critical role in heterogeneous diseases like schizophrenia and are considered to be highly promising and informative in treatment selection. In this study, homocysteine is evaluated in response to antipsychotic treatment.

Homocysteine appears to have a key role in the etiology and pathology of schizophrenia. Altered homocysteine metabolism implicated in schizophrenia interferes with normal methylation and leads to neuroexcitotoxicity (NMDA-mediated), vascular damage, oxidative stress, inflammation, apoptosis, and activation of mitochondrial dysfunction.¹⁸

Elevated homocysteine levels also contribute to cognitive impairment, beta-amyloid, and endothelial dysfunction, while hypohomocysteinemia benefits in reducing DNA methylation and oxidative stress.¹⁹ Homocysteine is one of the easily measurable biomarkers; establishing its relationship with response to antipsychotics is vital.

Personalized medicine is a promising medical method that divides patients into groups and tailors medical decisions, practices, therapies, and/or products to each patient's anticipated response or illness risk based on molecular techniques.²⁰ Antipsychotic treatment is associated with a lag period of 2–4 weeks; during this phase of treatment patients may discontinue treatment prematurely, increase suicide risk, and worsen the clinical condition. Hence, to overcome these and minimize costs, it is desirable to know in advance whether a drug is effective and tolerable. This study will help in establishing a relationship between homocysteine (as a biomarker) and response to antipsychotic drugs, which will help for an individualized treatment approach in schizophrenia patients.

The present trial focused on establishing the relation between homocysteine levels in peripheral blood and treatment outcomes with haloperidol and olanzapine in schizophrenia. The primary objective of this study is to compare the efficacy of olanzapine and haloperidol in schizophrenia patients and to estimate the relation of the biomarker homocysteine and clinical improvement of symptoms which will be predictive of future response to antipsychotics (“predictors”). The secondary objective is to assess the safety of study drugs.

Materials and Methods

Study Subjects

This trial was performed by the pharmacology department in collaboration with the Department of Psychiatry. Forty participants with newly diagnosed schizophrenia were recruited from the Department of Psychiatry at a tertiary care hospital from December 2018 to May 2019. Ethical approval for this study was obtained from Institutional Ethics Committee (IEC/18/JUL/142/26). The study was also registered in the clinical trial registry of India (CTRI), Government of India, with registration number CTRI/2018/11/016425. Informed consent and trial were in accordance with Good Clinical Practice procedures and Declaration of Helsinki (2013).

All the eligible participants were informed about the purpose and requirement of the study, the drug, efficacy, and safety points. Written informed consent was obtained in the local language—Tamil, from each study participant. Illiterate study participants gave their fingerprints after explaining the nature of the study. A Legally Acceptable Representative provided consent if the participant (vulnerable population) could not do so. A case report form was prepared and data was recorded.

Participants in the trial were notified of their withdrawal at any stage of the trial without explaining the reason, and they were not denied the opportunity of receiving adequate medical care in the institute while doing so. Any adverse events were asked to be reported by the study participant to the investigator immediately and were followed as per standard operating procedures of the Institutional Ethics Committee.

Eligibility Criteria

Study participants were diagnosed by the Positive and Negative Syndrome Scale (PANSS) criteria for schizophrenia (minimal, mild, and moderate) using structured clinical interviews.²¹ Participants of either sex aged between 15 and 45 years and newly diagnosed with schizophrenia (minimal, mild, and moderate) by PANSS criteria were included in the study. Known cases of allergic reactions to olanzapine or haloperidol, liver failure, kidney failure, pregnant women, lactating mothers, and participants enrolled in other investigational drug trials were excluded from the study.

Study Design

This was an open-label, prospective, randomized, parallel-group interventional trial. The sample size was calculated based on the prevalence (70%) of the previous study²²; the total estimated sample size was 40 for this pilot trial. Participants were randomized into two groups by computer randomization software (R software).²³

This was a double-arm study comprising 20 patients in the olanzapine group (group O) who received olanzapine (Sun Pharma, India) 5 mg per oral once daily after food and 20 patients in the haloperidol group (group H) received haloperidol (Sun Pharma, India) 10 mg per oral once daily after food.

Outcomes

Primary outcome measures were clinical improvement of symptoms assessed by the change from baseline to day 14 and day 28 of treatment using the Brief Psychiatric Rating Scale (BPRS)²⁴ and change in the homocysteine level from baseline to day 14 and day 28 of treatment. The secondary outcome measures were extrapyramidal symptoms assessed on baseline visit and compared on day 14 and day 28 of treatment using the Abnormal Involuntary Movement Scale (AIMS),²⁵ and safety in terms of adverse effects was evaluated by the occurrence of any symptoms and altered lab parameters.

The vitals were measured at every visit, and BMI was noted on day 0, day 14, and day 28 following standard procedures.²⁶ The sample collection, and lab parameters were evaluated using standard methods, such as CBC with UniCel DxH 800 (Beckman Coulter, Brea, CA, USA),²⁷ serum homocysteine (Architect i1000 SR, Abbott, USA),²⁸ serum RBS, and serum TGL (Beckman Coulter, Inc, Brea, CA, USA).²⁹

ECG was recorded on day 0 and after six months of treatment. The corrected QT interval was calculated using the formula described by the Bazett formula.³⁰ Adverse events were assessed using the WHO-Uppsala Monitoring Centre.³¹

Statistical Analysis

The data analysis was carried out on the Windows version of the SPSS Program 17.0. Descriptive statistics were used to summarize demographic as well as baseline variables. Mean and Standard deviation were calculated for continuous data, while absolute frequencies and percentages were calculated for categorical data. Means of study parameter were compared among the study groups using one-way ANOVA test. BMI, BPRS, AIMS, ECG, and adverse events were analyzed using the chi-square test. $P < .05$ was considered statistically significant for all results. Spearman Rank Correlation Test was used to establish a relation between BPRS and homocysteine. All investigations adhered to the intention-to-treat (ITT) concept. The ITT included all schizophrenia patients who met the inclusion criteria.

Results

This study assessed 42 newly diagnosed schizophrenia patients for eligibility criteria. The enrollment, allocation, follow-up, and analysis were depicted in the CONSORT 2010 flow chart (Figure 1). Forty patients were randomized into two groups. The demographic details of the participants in the two groups were analogous. The mean age was analogous among the groups, and male preponderance was seen in both groups (Figure 2A). Occupation details showed unemployment in the majority of the patients of both groups. The lifestyle habits like smoking and alcohol were minimum among the study population of both groups. Vitals were within normal reference ranges (Table 1).

The mean BMI showed that the patients of group O and group H had normal body weight at baseline. But it has gradually increased in patients of the group O during treatment, while with haloperidol, there was an initial rise during the first two weeks, and later it remained insignificant (Figure 2B).

The mean serum TGL and ECG of patients in both groups were comparable at baseline. The mean serum TGL in patients of group O significantly increased from baseline to 6 months of treatment, while it was insignificant from baseline to 6 months with haloperidol treatment (Figure 2C). The QTc interval abnormality was seen more in group O patients after 6-months of treatment (Figure 2D).

The psychiatric symptoms revealed through the BPRS score were predominantly moderate in the group O patients and mild in the group H patients but statistically insignificant at baseline. After treatment, the patients exhibited scores of mild symptoms in both groups. Forty percent of patients in

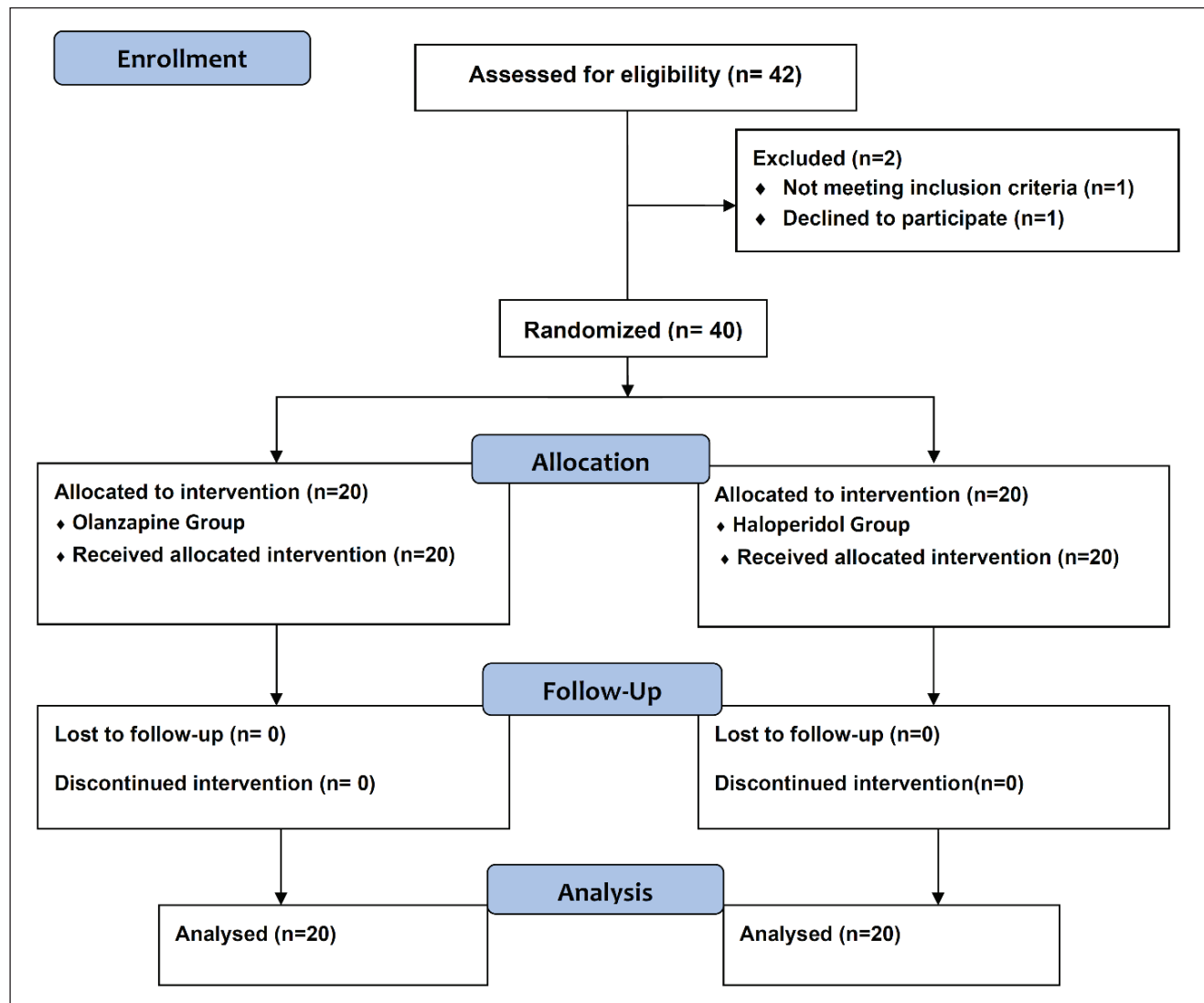


Figure 1. CONSORT 2010 Flow Chart.

group O showed absolutely zero scores after treatment (Figure 2E). EPS was assessed in both groups using the AIMS score, and a significant increase in the score was observed in group H on day 14 and day 28. In group O, these EPS symptoms were not present on day 14 but were observed in 1% of participants on day 28 (Figure 2F, Figure 2G).

The mean homocysteine levels were reduced in the group O patients (baseline = 13.91 ± 0.47 vs day 28 = 9.74 ± 0.5 $\mu\text{mol/L}$) than in group H patients (baseline = 13.97 ± 0.4 vs day 28 = 13.58 ± 0.39 $\mu\text{mol/L}$). The correlation between BPRS and homocysteine was established. The percent change in BPRS and homocysteine were correlated in the 40 participants. From the Spearman correlation coefficient ($r = -0.66$), it is inferred that as the symptoms of BPRS improve, there is an

increase in the difference between homocysteine compared to the baseline level (Figure 2H).

Comparison between mean serum homocysteine in the group O (mean change = 0.12) and homocysteine in the group H (mean change = 0.08) was significant (P value = 0.001). This shows that the mean change of homocysteine levels in group O is better compared to group H (Figure 2I).

In our study, there were no serious adverse events. However, headache, abdominal pain, and fatigue were reported. All adverse events were evaluated as per the WHO-UMC scale, and the ADR assessment is possible. All adverse events are reported to the ADR monitoring center as per the standard operating procedure of the Institution Ethics Committee.

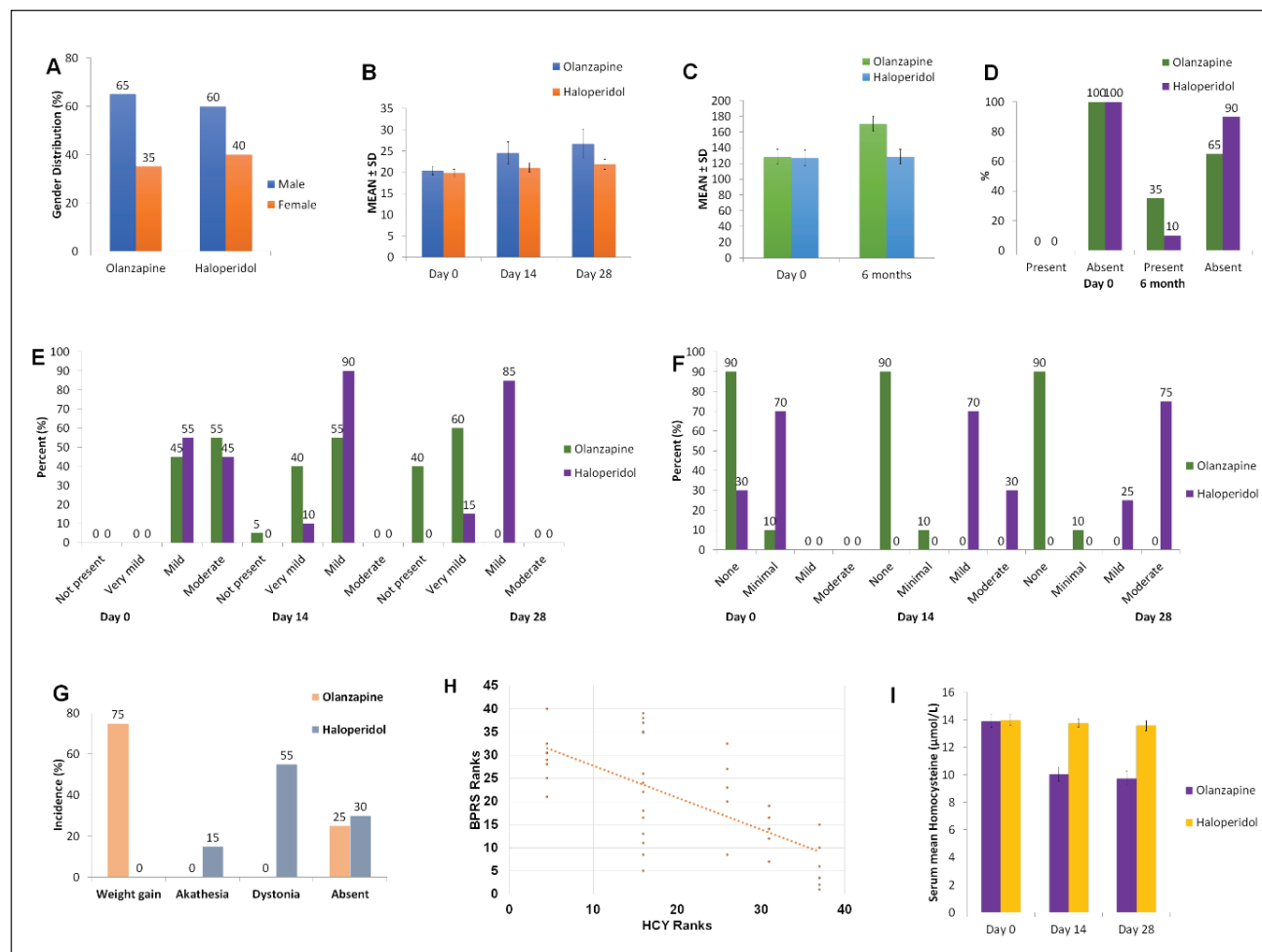


Figure 2. Clinical and biochemical parameters. (A) Gender distribution; (B) BMI changes between the groups during the study period; (C) Triglycerides; (D) QTc changes; (E) Brief Psychiatric Rating Scale scores of study group patients during the study period; (F) Abnormal Involuntary Movement Scale scores between groups; (G) Adverse drug reaction; (H) Correlation between homocysteine and BPRS scores among the study subjects; (I) Changes in homocysteine levels between groups.

Table 1. Demographic and Baseline Details of the Study Participants.

Parameter	Olanzapine Group (N = 20)	Haloperidol Group (N = 20)
Age, mean (SD)	34.40 (11.37)	37.05 (13.21)
Gender, n (%)		
Male	13 (65)	12 (60)
Female	7 (35)	8 (40)
BMI (kg/m ²), mean (SD)	20.37 (1.04)	19.77 (0.91)
Occupation, n (%)		
Employed	9 (45)	5 (25)
Unemployed	11 (55)	15 (75)
BPRS score, n (%)		
Not present	0 (0)	0 (0)
Very mild	0 (0)	0 (0)
Mild	9 (45)	11 (55)
Moderate	11 (55)	9 (45)

(Table 1 continued)

(Table 1 continued)

Parameter		Olanzapine Group (N = 20)	Haloperidol Group (N = 20)
Homocysteine ($\mu\text{mol/L}$), mean (SD)		13.91 (0.48)	13.97 (0.40)
AIMS score, n (%)	None	20 (100)	20 (100)
	Minimal	0	0
	Mild	0	0
	Moderate	0	0
Triglyceride (mg/dL), mean (SD)		128.50 (9.36)	127 (9.93)
ECG (QTc), n (%)	Normal	20 (100)	20 (100)
Alcoholic, n (%)		4 (20)	2 (10)
Smoker, n (%)		4 (20)	4 (20)
Suicidal tendency/attempt, n (%)		2 (10)	6 (30)
Family history, n (%)		2 (10)	4 (20)

Discussion

Although there is a symptomatic improvement in the current scenario, there is no full recovery in schizophrenia patients. This may be determined by using standardized treatment algorithms and estimation of biomarker levels. This can be done by incorporating biomarker evaluation in the standard treatment guidelines for faster recovery and effective treatment. Biomarker levels can be assessed at baseline and in the early course of treatment, both these levels are compared, and this method predicts treatment outcome and guides future treatment plans in the patient.³² Our study investigated the effectiveness and tolerability of olanzapine versus haloperidol in individuals with schizophrenia, as well as the relationship between homocysteine and treatment response. In our study, demographic details indicate that schizophrenia is common in males and unemployed adult age groups. Participants were diagnosed and enrolled based on PANSS criteria. Vitals were normal in all study participants. The severity of symptoms evaluated with BPRS was either score 3 (mild) or score 4 (moderate). Other baseline blood parameters, BMI, and ECG were normal in all study participants.

Several studies revealed that there is a strong causal relationship between plasma homocysteine and schizophrenia.^{33, 34} On the contrary, homocysteine levels in schizophrenia patients compared to controls were found to be comparable.³⁵ Recently, the association between homocysteine level and schizophrenia was found using the PANSS, Global Assessment of Functioning scale, and the Clinical Global Impression scale for clinical measurements.³⁶ Similarly, other studies newly introduced the effect of antipsychotic drugs on biomarkers in schizophrenia patients.³⁷⁻³⁹ The effect of olanzapine on homocysteine levels post-treatment at the 10th week in schizophrenia patients and their clinical relation using BPRS was that olanzapine significantly decreases homocysteine levels and clinically improved symptoms of schizophrenia. But this effect was not compared with a

standard drug.⁴⁰ BPRS score has also been used by other studies to evaluate the clinical improvement at different time points in schizophrenia patients.^{41, 42}

In our study, we used the BPRS score to compare the efficacy of olanzapine and haloperidol in schizophrenia patients by intergroup and intragroup analysis. BPRS scores improved more quickly with olanzapine than with haloperidol. As an outcome of these findings and improvement in clinical manifestations, it is evident that olanzapine is more beneficial than haloperidol.

The mean homocysteine levels declined more in group O compared to group H. Also, in our study, the correlation between BPRS and homocysteine was established. The changes in BPRS and homocysteine were correlated in the 40 participants. A negative correlation was seen between BPRS scores and serum homocysteine levels. Hence, it indicates that homocysteine can be used as a reliable biomarker to assess treatment response in schizophrenia patients. Also, the mean change of homocysteine levels is effective in group O in comparison to group H. Hence, evaluation of homocysteine as a biomarker can be used as a predictor of treatment outcome in schizophrenic patients.

Therefore, a biomarker can be used to change the line of treatment from an ineffective treatment to a better option in the early phase of treatment initiation, which can henceforth shorten the treatment duration and provide a better treatment regimen to the patient. Our findings infer that homocysteine has a good potential to predict the treatment response of antipsychotic drugs in most schizophrenia patients. Further studies are needed to evidence the accurate role of this biomarker in the mechanism of action of antipsychotic drugs in schizophrenia patients and can hence be taken forward in clinical practice.

Several studies have assessed adverse effects of antipsychotic drugs such as drug-induced EPS with increased AIMS score,⁴³⁻⁴⁵ obesity with olanzapine,⁴⁶ increased TGL levels with olanzapine,⁴⁷⁻⁴⁹ and ECG(QTc) changes more with olanzapine.^{50, 51}

In our study, we focused on four parameters to examine the safety of olanzapine and haloperidol in schizophrenia patients. These include extrapyramidal symptoms (AIMS score), BMI, TGL, and ECG changes. These parameters were evaluated at different time points, that is, AIMS score and BMI on day 0, day 14, and day 28, and TGL and ECG change on day 0 and sixth month. EPS was assessed in both groups using the AIMS score, and a significant increase in the score was observed in group H. There was an increase in the BMI value from baseline in participants treated with haloperidol, but it did not cross the normal BMI range. In group O patients, a marked increase in BMI was observed, indicating overweight as per BMI reference ranges. The mean BMI in group O has gradually raised during treatment. The TGL levels increased significantly from baseline to 6 months in participants on olanzapine but not in participants on haloperidol treatment. ECG changes were observed in seven study participants on olanzapine and two on haloperidol in the sixth month of treatment. All these results, which were used to compare safety parameters in both groups, were statistically significant.

In our study, group H participants developed mild and moderate EPS, respectively. In group O, these EPS symptoms were significantly low. As a consequence, drug-induced EPS in group H outnumbered those in group O. Seventy-five percent of patients in group O gained weight that was above the normal BMI level. The presence of an increase in BMI is an important risk factor for cardiovascular disease and diabetes mellitus.⁵² According to our findings, olanzapine causes weight gain in schizophrenic patients, which might be implicated in the development of cardiovascular disease. However, more research is warranted to fully comprehend its long-term cardiac safety profile. Sixty percent of patients treated in group O showed elevated TGL levels in the sixth month. QTc prolongation was observed in 35% and 10% of participants on olanzapine and haloperidol, respectively, in the 6th month of treatment. QTc prolongation exceeding a normal level (<440 ms) may increase the risk of ventricular tachyarrhythmias, especially torsade de pointes, and, therefore, sudden cardiac death in schizophrenia patients.⁵³ Though olanzapine decreased homocysteine levels in group O patients, it showed cardiovascular toxicity, which may be attributed to other mechanisms of olanzapine like cyclic adenosine monophosphate, adrenergic α -1 blockade, eosinophilia, and orthostatic hypotension-induced tachycardia.⁵⁴⁻⁵⁹

Our study did not observe other unwanted symptoms such as gynecomastia, galactorrhea, menstrual irregularities, and sexual dysfunction. Neutropenia and agranulocytosis were also not observed in our study. But two participants in group O showed an increase in RBS in the sixth month of treatment. Hence regular monitoring of RBS is needed for patients on olanzapine. All participants well tolerated these adverse effects, and there was no need for any medication. Vitals were also documented at every visit and were within normal limits

with no variations. Despite the metabolic adverse effects, group O has a lower EPS, which appears to be a safety benefit in patients undergoing schizophrenia treatment.

Limitations

This trial was done only in mild to moderate cases of schizophrenia, and severe cases were excluded from this trial. It was an open-label study which could be a source of bias that can be overcome by a similar double-blinded study.

Conclusion

Olanzapine is more efficacious than haloperidol in schizophrenia patients, and in terms of safety, both drugs have adverse effects. Homocysteine was used as the biomarker in our study. In both the treatment groups, there was a decrease in homocysteine levels at different time points. But homocysteine levels were reduced in olanzapine group. Thus, antipsychotic drugs might have the potential to modulate this protein which has a role in the pathogenesis of schizophrenia. Therefore, homocysteine may be used as an easily measurable and potent biomarker to predict and assess treatment response in schizophrenia patients.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

Not applicable

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Informed Consent

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