

## Efficacy and Tolerability of Clozapine versus Quetiapine in Treatment-resistant Schizophrenia

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### ABSTRACT


**Objectives:** To compare the efficacy and tolerability of clozapine and quetiapine in patients with treatment-resistant schizophrenia (TRS). **Patients and Methods:** In this prospective, randomized, open label study of 14 weeks, 53 patients with schizophrenia diagnosed as per ICD-10 and fulfilling the modified version of Conley and Kelly's criteria of TRS were randomly assigned to receive clozapine or quetiapine as per a computer-generated random table. After 2-weeks of dose-titration phase, doses were fixed at minimum therapeutic dose and subsequently adjusted according to the clinical improvement. All patients received dosage of respective drug in therapeutic range. 13 patients were lost to follow up. Treatment efficacy and side effects were evaluated with standardized rating scales. **Results:** Clozapine group (reduction in total score: mean=14.45, SD=10.39) had significantly greater reductions ( $P=0.004$ ; CI=3.541-17.059) in the Positive and Negative Syndrome Scale (PANSS) total score, PANSS positive subscale and PANSS general psychopathology subscale at 14 weeks in comparison to the quetiapine group (reduction in total score: mean=4.15, SD=10.71). Significant reduction in PANSS negative subscale was seen with both drugs but no significant difference was present between the two drugs. At 14 weeks, 30% patients in clozapine group and 15% patients in quetiapine group showed response. Clozapine led to significantly greater side effects ( $P<0.001$ , CI=2.241-6.059) on Glasgow Antipsychotic Side-effect Scale (GASS) than quetiapine. **Conclusions:** Clozapine was found to be more efficacious than quetiapine in patients with TRS but was associated with greater side effects. Both the drugs were found to be equally effective in reducing the negative symptoms.

**Key words:** Clozapine, quetiapine, treatment-resistant schizophrenia

### INTRODUCTION

Schizophrenia carries a high degree of disability, which accounts for 0.5% of the disability-adjusted life years.<sup>[1]</sup> Antipsychotic is the main-stay of treatment for people with schizophrenia, and yet approximately one-fifth to

one-third of patients with this disorder are resistant to drug treatment.<sup>[2]</sup> Clozapine has been found to be effective in treatment-resistant schizophrenia (TRS)<sup>[3,4]</sup> and it was approved for TRS by the Food and Drug Administration in 1989. However, approximately 40%–70% of

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neuroleptic-resistant patients with schizophrenia are nonresponders even to clozapine.<sup>[5]</sup> Moreover, with clozapine exists a risk of agranulocytosis.<sup>[3,4]</sup> Quetiapine, with structural analogy to clozapine, but with molecular discrepancies explaining the lack of agranulocytosis risk<sup>[6]</sup> seems to be an alternative in TRS. There are a few studies showing the efficacy of quetiapine in the treatment of schizophrenia resistant to previous antipsychotics,<sup>[7]</sup> but the findings have not been replicated in other studies, and there is a dearth of such studies carried out on the Indian population. Thus to look at an alternative treatment regimen for TRS, this study was a logical outcome where the authors set out to address some unanswered queries.

## METHODS

Patients who came to the Department of Psychiatry of Government Medical College and Hospital (GMCH), Chandigarh, India were considered for the study. They were 18–65 years, met the International Classification of Diseases, Tenth Revision-Diagnostic Criteria for Research<sup>[8]</sup> criteria for schizophrenia, gave informed consent, were accompanied by the reliable informant and were enrolled in the study from December 2013 to June 2015.

For the study, modified version of Conley and Kelly's criteria<sup>[2]</sup> of TRS was used, which is defined as, "No clinical response with two different antipsychotics used separately in the dose range of 400–600 mg of chlorpromazine per day or equivalents for 6 weeks; no period of good social or occupational functioning at least in last 1 year, and a minimum clinical global impressions (CGIs) scale rating of 4 (moderately ill); Brief Psychiatric Rating Scale (BPRS) total score >45, and a score of >4 on 2 out of 4 positive items."

Patients with a history of treatment with clozapine and/or quetiapine in the past, having seizure disorder, heart conduction defects, history of agranulocytosis or total lymphocyte count <3500/cubic mm, diabetes mellitus, neurological disorders, head injury, movement disorder, lactating or pregnant women, comorbid substance dependence except nicotine and caffeine, subnormal intelligence and late-onset schizophrenia (after 45 years) were excluded.

This was a comparative, open-label, prospective interventional study. The patients were randomly assigned into two groups as: Group A (clozapine group) or Group B (quetiapine group) as per a computer-generated random table with an aim to recruit a minimum of twenty patients in each group and were followed up for 14 weeks after treatment initiation. The trial was registered with Clinical Trial Registry, India (CTRI Registration number CTRI/2016/02/006660).

The principles enunciated in the Declaration of Helsinki<sup>[9]</sup> and Indian Council of Medical Research<sup>[10]</sup> was complied with and the study was approved by the ethical review committee of the institution.

## Intervention

After recruitment, patients who were on antipsychotics were given a drug-free/washout period (1 week for oral; 1 month for long-acting depot preparation). The patients were randomly allocated to either of the Group A or B. The dosages of the drugs were kept in the therapeutic range of 150–450 mg/day for clozapine and 400–800 mg/day for quetiapine.<sup>[11]</sup> Clozapine was started with 25 mg/day in two divided doses and increased by 25 mg/day, whereas quetiapine was started at 50 mg/day in two divided doses and increased by 50 mg/day. The minimum therapeutic dose in all the patients was reached within 2 weeks of starting the treatment. After this, patients were continued on the same dose for 4 weeks. At the end of 4 weeks, if the improvement was not adequate (<50% reduction in Positive and Negative Syndrome Scale [PANSS]<sup>[12]</sup> score), the dose of the respective drug was further increased to the maximum permissible dose and the patients were re-assessed after 4 weeks and 8 weeks. Concomitant medications (like benzodiazepines for sleep disturbances, amitriptyline for hypersalivation, etc.) were permitted wherever required, and it was documented. Patients having serious adverse drug reaction were dropped from the study and managed as per the standard guidelines. Each patient's sociodemographic and clinical variables were recorded on prescribed Performa designed specifically for the study.

## Outcomes

Physical examination, body weight, height, QTc interval on electrocardiogram, blood chemistry, and complete hemogram were carried out at the baseline, 2<sup>nd</sup> week and thereafter every 4<sup>th</sup> week. In addition, total leukocyte count, differential leukocyte count, platelet count, absolute neutrophil count were done on a weekly basis for patients receiving clozapine. To ensure compliance in outpatients, a family member was entrusted to supervise the intake of the drug in their presence. In addition, the empty strips of medicines were shown to doctors during follow-up visits.

Patient's clinical status was assessed with BPRS<sup>[13]</sup> and CGIs<sup>[14]</sup> at baseline and PANSS<sup>[12]</sup> at baseline, 2, 6, 10, and 14 weeks. Side effects were assessed using the Glasgow Antipsychotic Side Effect Rating Scale (GASS)<sup>[15]</sup> at baseline and thereafter at 2, 6, 10, and 14 weeks.

## Statistical method

The statistical analysis included Chi-square test for qualitative data and ANOVA and MANOVA with

repeated measures for quantitative data. *T*-test was applied to compare individual assessments. Data were analyzed using SPSS version 17.0 (Version 17.0, IBM) and it was represented in mean and standard deviation (SD) where data were skewed, nonparametric test (Mann–Whitney test) was used. Significance level was  $P < 0.05$ .

## RESULTS

A total of 72 patients were screened initially, of which 19 patients were excluded due to various reasons. Remaining 53 patients were enrolled in the study. Subsequently, 13 patients dropped out of the study after the first assessment (four in Group A; nine in Group B). From among the dropouts, six patients dropped out

due to the lack of efficacy (one in Group A and five in Group B), three patients dropped out due to poor compliance (one in Group A and two in Group B), two patients dropped out due to intolerability of drug (one in each group) and two patients could not be contacted (one in each group). Finally, forty patients (twenty patients in each group) completed all assessments and were included in final analysis.

### Comparison between clozapine (Group A) and quetiapine (Group B) group on sociodemographic and clinical variables

The patients in clozapine and quetiapine group did not differ significantly on sociodemographic variables, diagnosis, and clinical characteristics, i.e., total duration of illness, BPRS score, PANSS total scores, positive

**Table 1: Comparison between clozapine (Group A) and quetiapine (Group B) group on sociodemographic and clinical variables**

Variable	Group A (n=20)	Group B (n=20)	Significance (P)	95% CI	
				Lower	Upper
Age, mean (SD)	39.40 (7.46)	39.40 (6.82)	1.000	NA	NA
Sex (%)					
Male	13 (65.0)	14 (70.0)	0.736	NA	NA
Female	7 (35.0)	6 (30.0)			
Area (%)					
Rural	6 (30.0)	7 (35.0)	0.736	NA	NA
Urban	14 (70.0)	13 (65.0)			
Education (%)					
Below matric	8 (40.0)	7 (35.0)	0.744	NA	NA
Matric and above	12 (60.0)	13 (65.0)			
Occupation (%)					
Working	3 (15.0)	2 (10.0)	0.633	NA	NA
Nonworking	17 (85.0)	18 (90.0)			
Income (%)					
<5000	7 (35.0)	10 (50.0)	0.264	NA	NA
5001-10,000	2 (10.0)	4 (20.0)			
>10,000	11 (55.0)	6 (30.0)			
Family (%)					
Nuclear	12 (60.0)	12 (60.0)	1.000	NA	NA
Joint	8 (40.0)	8 (40.0)			
Marital status					
Single	8 (40.0)	8 (40.0)	1.000	NA	NA
Ever-married	12 (60.0)	12 (60.0)			
Diagnosis (%)					
F20.0	10 (50.0)	14 (70.0)	0.611	NA	NA
F20.1	2 (10.0)	1 (5.0)			
F20.2	1 (5.0)	1 (5.0)			
F20.3	7 (35.0)	4 (20.0)			
Total duration of illness (years)	14.35 (3.91)	13.80 (3.89)	0.658	-1.95	3.05
BPRS	58.75 (3.96)	58.20 (5.00)	0.702	-2.34	3.44
CGI (severity of illness)	4.95 (0.22)	4.80 (0.41)	0.162	-0.064	0.364
PANSS positive symptoms	26.00 (3.08)	24.05 (4.30)	0.107	-0.443	4.343
PANSS negative symptoms	26.65 (3.76)	26.00 (4.18)	0.608	-1.895	3.195
PANSS general psychopathology symptoms	52.90 (5.79)	51.35 (8.24)	0.496	-3.010	6.110
PANSS total	105.45 (8.57)	101.30 (12.06)	0.217	-2.546	10.846
GASS	3.20 (1.36)	3.30 (1.30)	0.814	-0.953	0.753

CI – Confidence interval; BPRS – Brief Psychiatric Rating Scale; CGI – Clinical global impression; PANSS – Positive and Negative Syndrome Scale; GASS – Glasgow Antipsychotic Side-effect Rating Scale; SD – Standard deviation; NA – Not applicable

subscale scores, negative subscale scores, and general psychopathology subscale scores and CGI (severity of illness) and GASS score [Table 1].

### Drug efficacy

Twenty percent reduction in psychopathology score was taken as a response in the study.<sup>[3,7]</sup> In our study, six patients (30%) in clozapine group and three patients (15%) in quetiapine group showed a response (>20% reduction in PANSS from baseline) at the endpoint, i.e., 14 weeks. However, the difference between the two groups was not significant ( $P = 0.256$ ).

### Comparison of Positive and Negative Syndrome Scale scores of two groups across assessments

On within group analysis while there was statistically significant improvement in positive, negative, general subscale, and total score of PANSS in clozapine group, with regards to quetiapine such improvement, was present only in negative subscale of PANSS [Table 2].

### Change in Positive and Negative Syndrome Scale scores for clozapine and quetiapine group

At the end of 14 weeks, the patients assigned to clozapine had significantly greater reductions in the PANSS total score (mean = 14.45, SD = 10.39) than the patients assigned to quetiapine (mean = 4.15, SD = 10.71,  $P = 0.004$ ). A similar significantly greater reduction in clozapine group was seen on the PANSS positive subscale and PANSS general psychopathology subscale. However, on the negative subscale of PANSS, there was a significant reduction with both clozapine and quetiapine and the difference between two drugs was not significant [Tables 2 and 3].

### Comparison of the side-effects in clozapine (Group A) and quetiapine (Group B) group

There was statistically significant increase in GASS score at 6, 10, and 14 weeks from baseline in both groups [Tables 4 and 5]. However, while comparing the two drugs, a statistically significant difference was seen at week 6, 10, and 14 and quetiapine was found to be superior to clozapine in terms of side-effect profile. The most common side effects observed in clozapine group were increased sleepiness/sedation (65%), feeling drugged (60%), drooling of saliva at night (45%) and dizziness (35%) and weight gain (45%). The most common side effects noted in quetiapine group were dry mouth (50%), difficulty in passing urine (45%), sleepiness/sedation (35%), dizziness (30%), and weight gain (20%).

## DISCUSSION

To the best of our knowledge, this is the first Indian study carried out to compare the efficacy and tolerability of clozapine and quetiapine in TRS. Forty patients who completed all four assessments were included in the final analysis. The two groups were comparable at baseline on sociodemographic and clinical variables. The mean dose of clozapine was 322.50 mg/day, and quetiapine was 790.0 mg/day.

### Clozapine group

In this study, 6 (30%) patients in clozapine group showed response. This finding concurs with the multi-centric study conducted by Kane *et al.* which established clozapine as preferred drug for TRS<sup>[3]</sup> and another large randomized double-blind comparative study of clozapine and haloperidol in patients of refractory schizophrenia in which superior improvement was

**Table 2: Comparison of Positive and Negative Syndrome Scale scores of two groups (Group A - clozapine; Group B - quetiapine) across assessments**

PANSS	Mean (SD)							
	Positive		Negative		General		Total	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
Baseline	26.00 (3.08)	24.05 (4.30)	26.65 (3.76)	26.00 (4.18)	52.90 (5.79)	51.35 (8.24)	105.45 (8.57)	101.30 (12.06)
14 <sup>th</sup> week	21.85 (4.49)	23.60 (6.02)	22.45 (4.16)	23.00 (4.61)	46.70 (5.54)	50.60 (10.03)	91.00 (10.41)	97.15 (17.84)
Baseline versus 14 <sup>th</sup> week ( $P$ )	<0.001	1.000	<0.001	<0.001	<0.001	1.000	<0.001	0.597

PANSS – Positive and Negative Syndrome Scale; SD – Standard deviation

**Table 3: Reduction in scores from baseline on Positive and Negative Syndrome Scale for clozapine (Group A) and quetiapine (Group B) group**

PANSS	Mean (SD)		Significance ( $P$ )	95% CI	
	Group A	Group B		Lower	Upper
Reduction in PANSS					
Positive	4.15 (3.69)	0.45 (3.82)	0.003	1.296	6.103
Negative	4.20 (2.28)	3.00 (2.38)	0.112	-0.294	2.695
General psychopathology	6.20 (5.38)	0.75 (5.94)	0.004	1.824	9.076
Total score	14.45 (10.39)	4.15 (10.71)	0.004	3.541	17.059

PANSS – Positive And Negative Syndrome Scale; SD – Standard deviation; CI – Confidence interval



**Table 4: Comparison on Glasgow Antipsychotic Side-effect Scale between two groups (Group A - clozapine, Group B - quetiapine)**

Assessment	Mean (SD)		Significance (P)	95% CI	
	Group A	Group B		Lower	Upper
Baseline	3.20 (1.36)	3.30 (1.30)	0.814	-0.953	0.753
6 weeks	12.50 (3.40)	7.25 (2.12)	<0.001 <sup>#</sup>	3.437	7.063
10 weeks	14.20 (2.70)	9.55 (1.57)	<0.001 <sup>#</sup>	3.233	6.067
14 weeks	14.80 (3.74)	10.65 (1.95)	<0.001 <sup>#</sup>	2.241	6.059

<sup>#</sup>Skewed data, P value calculated with nonparametric tests.  
SD – Standard deviation; CI – Confidence interval

**Table 5: Effects of clozapine (Group A) and quetiapine (Group B) across assessments on Glasgow Antipsychotic Side-effect Rating Scale**

Group	P		
	Baseline versus 6 weeks	Baseline versus 10 weeks	Baseline versus 14 weeks
Group A	<0.001	<0.001	<0.001
Group B	<0.001	<0.001	<0.001

observed in the clozapine group.<sup>[16]</sup> Significantly, more patients in clozapine group had  $\geq 20\%$  reduction in symptoms than the comparator drugs in both these studies.<sup>[3,16]</sup> The response rate of 30% with clozapine in this study is somewhat similar to these two studies.

The superiority of clozapine over typical and atypical antipsychotics has been reported in some systematic reviews and meta-analysis. However, studies comparing clozapine with quetiapine were not included in these. Furthermore, there was a high degree of heterogeneity in terms of duration of the study, dosage of drugs used, level of resistance to previous treatment and financial support from a drug company among various studies included in these systematic reviews and meta-analysis, and hence it may not be appropriate to include these studies in a meta-analysis.<sup>[4,17-19]</sup>

### Quetiapine group

In this study, patients with quetiapine had significant improvement only in negative symptoms and overall 3 (15%) patients showed response. These findings are in contradiction to an earlier study on 95 TRS patients, wherein 59% of quetiapine-treated patients were defined as PANSS responders compared to 38% of haloperidol-treated patients and quetiapine showed numerically greater but nonsignificant improvement at 8 weeks in all subscales and total score of PANSS in comparison to haloperidol.<sup>[7]</sup> The reason for greater improvement could be the inclusion of mildly ill patients (score of 3 or more on CGI), whereas all the patients in our study were moderately ill (score of 4 or more on CGI) and lower degree of treatment resistance. Findings of this study are also inconsistent with the findings of a smaller 4-week study which showed

response in 50% of the cases as well as significant reduction in total PANSS scores in patients who were refractory to first-generation antipsychotics and were later treated with quetiapine.<sup>[20]</sup> Reasons for higher response rate in that study could be lower degree of treatment resistance, small sample size, single-blind design which can lead to bias. Moreover, unlike the current study, this study did not have a comparator group. The response rate to typical and atypical antipsychotics in other studies has not been as high as reported in the above-mentioned two studies.<sup>[3,16,21-23]</sup>

### Clozapine versus quetiapine group

In this study, the difference between clozapine and quetiapine in term of response rate was not statistically significant which can be attributed to a smaller sample size of this study.

Patients assigned to clozapine had significantly greater reductions on positive symptoms, general psychopathology and total PANSS score than the patients assigned to quetiapine. However, there was no significant difference between the two groups so far as reduction in negative symptoms was concerned; both drugs produced significant improvement in negative symptoms from the baseline assessment. These results are consistent with Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Phase 2 investigations, where patients assigned to clozapine had significant reductions in the PANSS total score and PANSS general psychopathology subscale than the patients assigned to quetiapine. Reductions in positive and negative subscale scores in clozapine group were greater than quetiapine, but it was not statistically significant in that study.<sup>[24]</sup> Another noncommercially funded, pragmatic, open, multisite, and randomized controlled trial comparing clozapine with other SGA (including quetiapine) showed that the improvement seen in clozapine group was significantly higher in comparison to SGA group at 12, 26, and 52 weeks, although authors did not publish results for the different SGA.<sup>[25]</sup>

However, findings of this study should be interpreted carefully because clozapine is associated with sedation, hyper-salivation, orthostatic hypertension and metabolic side effects<sup>[24,26]</sup> leading to poor tolerability. Other serious side effects such as agranulocytosis,<sup>[27]</sup> seizure,<sup>[28]</sup> and myocarditis<sup>[29]</sup> have been reported in the literature. Further important limitation arises from the need of slow titration and weekly blood counts which are laborious.<sup>[30]</sup> In addition, a significant proportion of TRS population is nonresponder to even clozapine.<sup>[5]</sup> Thus, there is still a prospect for using other molecules when clozapine is ineffective or intolerable though uncertainty exists regarding which molecule should be used in such a scenario.<sup>[30]</sup>

Negative symptoms predominate major portion of the course of illness and account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.<sup>[31-33]</sup> In such a scenario, quetiapine can be considered as a viable alternative as it showed a response in 15% of patients and was associated with significant improvement in negative symptoms. In fact, a metaanalysis conducted by Cochrane Schizophrenia group has found quetiapine to be more efficacious than clozapine on the negative symptom subscore.<sup>[34]</sup>

The current study found that quetiapine was better so far as side effects of the two drugs were concerned as reflected by the GASS score. In addition, the side effects of both the drugs were mild in severity as only one patient in each group had dropped out due to side effects. However, the retention rate was better in the clozapine group as 4 patients dropped out from this group as compared to 9 patients in the other group. Clozapine was associated with sedation, hyper-salivation, and weight gain in greater proportion of the patients, whereas quetiapine caused anticholinergic side effects (dry mouth, difficulty in passing urine, etc.) in more number of patients and this finding are consistent with previous CATIE trials.<sup>[24,26]</sup> The current study, in fact, showed greater anticholinergic side effects due to quetiapine compared to a previous industry-sponsored study.<sup>[35]</sup>

## CONCLUSION

Clozapine is still a good choice in TRS, and it was found to be more effective than quetiapine. However, clozapine was associated with greater side effects than quetiapine. Quetiapine, on the other hand, was also effective and equivalent to clozapine in the reduction of negative symptoms. Thus quetiapine might be a better choice in cases of TRS with predominant negative symptomatology, especially in instances where clozapine is ineffective or cannot be used.

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## Conflicts of interest

There are no conflicts of interest.

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