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Original Article

Comparative Outcomes of Clozapine Therapy in Early versus Late Initiators in Patients with Treatment-Resistant Schizophrenia

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ABSTRACT

Objective: To compare the outcomes of clozapine treatment in early initiators vs late initiators in patients with treatment-resistant schizophrenia

Study Design: Quasi-experimental study

Place and Duration of Study: Departments of Psychiatry Combined Military Hospital Peshawar and Combined Military Hospital Nowshera, Pakistan, from Jan 2023 to Mar 2024.

Methodology: The study included 103 patients with treatment-resistant schizophrenia, diagnosed by going over the past history and record, naive to clozapine, categorized into early (Group-A) and late (Group-B) initiators based on whether they started treatment within or after four years of diagnosis. Data was collected using a semi-structured questionnaire and Positive and Negative Syndrome Scale (PANSS) scores, with treatment efficacy evaluated via changes in these scores after three months using an independent t-test.

Results: Out of 103 patients 78(75.7%) were male and 25(24.3%) were female. The mean age of the participants was 31.49±9.06 years. Comparison of post-treatment PANSS scores between the two groups indicated a significant difference (p<0.001), suggesting that the timing of clozapine initiation impacts treatment outcomes.

Conclusion: Starting clozapine earlier in the course of illness is associated with improvement in symptoms.

Keywords: Clozapine Initiation, Initiators, Schizophrenia, Treatment Resistant Schizophrenia.

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INTRODUCTION

Treatment-resistant schizophrenia (TRS) is diagnosed when two different antipsychotics fail to work after proper trials, leading to significant challenges in patient outcomes and their social and occupational integration.[1] While almost half of those diagnosed with schizophrenia find relief with treatment, a significant portion of patients remain unresponsive to standard medications, and continue to suffer.[2] Clozapine is the preferred treatment for symptom remission in treatment-resistant schizophrenia, but its use is often delayed due to potential side effects, affecting patient outcomes significantly.[3] A study by 204 U.S. psychiatrists showed that TRS patients had higher unemployment, more hospitalizations, and greater comorbidity rates than non-TRS patients. Despite clozapine being the only approved drug for TRS, it was the fifth choice among psychiatrists who preferred adjusting doses or adding antipsychotics first.[4] Furthermore, a recent meta-analysis revealed that compared to second-generation antipsychotics, clozapine was linked with reduced rates of (re)hospitalization and all-cause discontinuation, in addition to improved overall symptom outcomes.[5] Another meta-analysis and systematic review showed that younger age, lower Positive and Negative Syndrome Scale (PANSS) negative scores, and paranoid schizophrenia subtype predict better clozapine response.[6] An audit assessing antipsychotic prescribing for TRS outpatients found that 43% received poly therapy, while only 19.6% were on clozapine.[7]

It has been shown that early clozapine use in TRS can achieve a 60-70% response, with benefits extending up to a year and significant symptom reduction by 12 weeks as a second- or third-line treatment.[8] Recent studies show that starting clozapine earlier and with fewer prior antipsychotic trials leads to improved outcomes in TRS patients.[9,10]

We conducted this study to compare the outcomes of clozapine treatment in early initiators vs late initiators in patients with treatment-resistant schizophrenia

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METHODOLOGY

This Quasi-experimental study was conducted at the Departments of Psychiatry Combined Military Hospitals Peshawar and Nowshera, Pakistan, from January 2023 to March after obtaining approved from the Ethical Committee (ref no: 03 Ethical Committee/DME dated 01-03-2024).

Inclusion Criteria: Clozapine naïve patients of either gender between 18 and 50 years of age presenting in the outpatient department with diagnosis of treatment resistant schizophrenia were included.

Exclusion Criteria: Patients with comorbid medical and surgical conditions, patients using drugs of abuse, and those having already used clozapine in the past were excluded.

The sample size was calculated using the WHO calculator, with anticipated population proportion of early initiators as 0.82, and late initiators as 0.32.[10] This came 19 patients in each arm. However, to maximize generalizability, it was decided to include 103 patients (51 and 52 patients in early vs late initiator group respectively). Using nonprobability sampling, patients were recruited and divided into early (Group-A) and late initiator (Group-B) groups based on a 4-year diagnostic threshold (Figure).

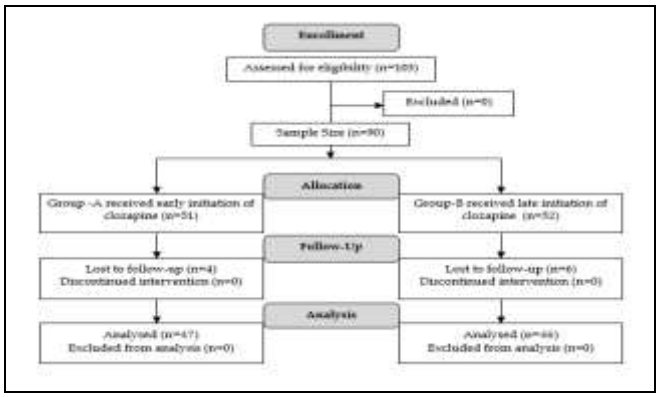

Figure: Patient Flow Diagram (n=103)

After taking informed consent, all patients were started on clozapine, with dosage adjustments every two weeks, and their symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) scale. Treatment effectiveness was analyzed by comparing changes in PANSS scores from baseline to three months post-treatment between and within both groups.

Using a semi-structured questionnaire, demographic data, including age, gender, educational status, marital status, employment status, and duration of illness, as well as treatment histories detailing previous medications and the timing of clozapine initiation, categorized into early and late initiation based on whether treatment started within or after four years of diagnosis, were noted. Pre-treatment PANSS scores were collected during the initial interview, while post-treatment scores were gathered during a follow-up visit.

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 27, with quantitative variables reported as median with IQR, qualitative variables as frequency and percentages. The Mann-Whitney U test was used to compare the differences in the reduction of PANSS scores between early and late initiators. Linear regression was used to assess the effect of multiple variables (confounders) on the outcome. A p value < 0.05 was considered as significant.

RESULTS

This study evaluated the demographic status of 103 patients, alongside response to clozapine treatment after three months among early (Group-A) and late (Group-B) initiator groups. Ten out of 103 patients were lost to follow-up, and the missing values were imputed for calculation purposes. Among the participants, 78(75.7%) were male and 25(24.3%) were female. The marital status distribution was 46(44.7%) single, 48(46.6%) married, and 9(8.7%) divorced. Employment status showed that 26(25.2%) were employed and 77(74.8%) were unemployed (Table-I).

Table-I: Demographic Variables of Participants (n=103)

	n (%)
Gender	
Male	78(75.7%)
Female	25(24.3%)
Marital status	
Single	46(44.7%)
Married	48(46.6%)
Divorced	9(8.7%)
Employment status	
Employed	26(25.2%)
Unemployed	77(74.8%)

The analysis of pre-treatment Positive and Negative Syndrome Scale (PANSS) scores between early and late clozapine initiators revealed no statistically significant difference. Pre-treatment, the median Positive Symptoms Score for early initiators was 30.0 (IQR 25.0–36.0) compared to 32.0 (IQR 27.0–35.0) for late initiators (p=0.463). The median Negative Symptoms Score was 27.0 (IQR 21.0–32.0) for early

initiators and 27.0 (IQR 22.0–34.0) for late initiators (p=0.522). The median General Score was 70.0 (IQR 65.0–80.0) for early initiators and 72.0 (IQR 65.0–79.0) for late initiators (p = 0.637). The Total Pre-treatment Score median (IQR) for early initiators was 130.0 (IQR 120.0–140.0) compared to 133.0 (IQR 123.0–143.0) for late initiators (p=0.476).

Post-treatment, the median Positive Symptoms Score for early initiators was 15.0 (IQR 11.0–20.0) and for late initiators was 22.0 (IQR 17.0–27.0), with p<0.001. The median Negative Symptoms Score was 16.0 (IQR 12.0–20.0) for early initiators and 19.0 (IQR 16.0–24.0) for late initiators (p=0.014). The median General Score was 40.0 (IQR 30.0–50.0) for early initiators and 55.0 (IQR 45.0–70.0) for late initiators (p<0.001). The Total Post-treatment Score median (IQR) was 70.0 (IQR 55.0–90.0) for early initiators and 95.0 (IQR 80.0–110.0) for late initiators (p<0.001). Post-treatment PANSS scores indicated a significant difference, suggesting that the timing of clozapine initiation impacts treatment outcomes (Table-II).

Table-II: Comparison of PANSS scores Pre and Post Treatment with Clozapine (n=103)

	Initiator type	n	Median (IQR)	*p* value
Positive Symptoms Score Pre treatment	Group-A	51	30.0(25.0 - 36.0)	0.463
	Group-B	52	32.0(27.0 - 35.0)	
Negative Symptoms Score Pre treatment	Group-A	51	27.0(21.0 - 32.0)	0.522
	Group-B	52	27.0(22.0 - 34.0)	
General Score Pre treatment	Group-A	51	70.0(65.0 - 80.0)	0.637
	Group-B	52	72.0(65.0 - 79.0)	
Positive Symptoms Score Post treatment	Group-A	47	15.0(11.0 - 20.0)	<0.001
	Group-B	46	22.0(17.0 - 27.0)	
Negative Symptoms Score Post treatment	Group-A	47	16.0(12.0 - 20.0)	0.014
	Group-B	46	19.0(16.0 - 24.0)	
General Score Post treatment	Group-A	47	40.0(30.0 - 50.0)	<0.001
	Group-B	46	55.0(45.0 - 70.0)	
Total Pretreatment Score	Group-A	51	130.0(120.0-140.0)	0.476
	Group-B	52	133.0 (123.0 - 143.0)	
Total Post treatment Score	Group-A	47	70.0 (55.0 - 90.0)	<.001
	Group-B	46	95.0(80.0-110.0)	
Time to clozapine initiation in years	Group-A	51	2.49(1.0 - 4.0)	<.001
	Group-B	52	9.90(6.0 - 14.0)	

**PANSS: Positive and Negative Syndrome Scale*

Regarding the patients lost to follow-up, 4 out of 51 early initiators (7.8%) and 6 out of 52 late initiators (11.5%) were lost to follow-up, with no statistically significant difference between the groups (p=0.764).

Analysis performed to explore the impact of confounding factors on treatment efficacy, indicated that early initiation of clozapine significantly predicted lower total post-treatment PANSS scores, suggesting better outcomes. Variables such as age, gender, marital status, and employment status did not significantly affect post-treatment scores. Additionally, delaying clozapine initiation was associated with higher post-treatment PANSS scores, indicating worse treatment outcomes. (Table-III)

Table-III: Multiple Linear Regression Analysis for Confounders

Variable	Unstandardized Coefficients		Standardized Coefficients	T	*p* value
	B	Std. Error	Beta		
(Constant)	76.427	11.296		6.766	<0.001
Age	-.224	0.421	-.122	-.532	0.596
Gender	-6.789	3.931	-.178	-1.727	0.88
Educational Status	1.673	2.258	.086	0.741	0.461
Marital Status	3.423	4.357	0.132	0.786	0.434
Employment Status	6.777	4.741	0.167	1.429	0.157
Initiator type	-12.149	5.783	-.359	-2.101	0.039

DISCUSSION

Clozapine was initially introduced in the 1960s but was later withdrawn due to its association with numerous fatalities.[11] The drug was reintroduced after a pivotal study showed that patients with schizophrenia, who did not respond to other medications, benefited from Clozapine.[12] Research indicates significant delays in initiating clozapine treatment, ranging from 5Click or tap here to enter text. to 16 years, with variations noted between New Zealand and the UK.[13,14] Limited data suggest that longer delays and older initiation ages increase clozapine non-adherence.[15] However, proactive interventions have reduced these delays to under 3 years.[16]

Our study has been the first of its kind addressing this issue in the military setups of Pakistan. Our findings suggest that initiating clozapine earlier is associated with more reduction in symptoms severity over a period of three months. A systematic review

found that delays in clozapine treatment for treatment-resistant schizophrenia (TR-SCZ) were linked to poorer outcomes.[17] These studies accounted for variables such as age, sex, and illness duration. Older age correlated with longer delays in clozapine initiation.[18] Our findings are consistent with this study as there has been lesser improvements in the delayed initiator group whilst taking into account the variables of age, sex, illness duration, marital and employment status. A recent study analyzing 105 patients with treatment-resistant schizophrenia (TRS) revealed that initiating clozapine within 2.8 years significantly improved symptoms, with a response rate of 81.6% compared to 30.8% when initiation is delayed beyond this period.10 Our study also showed that starting clozapine earlier was associated with increased improvement.

One study found that clozapine significantly improved employment rates and durations in treatment-resistant schizophrenia compared to other antipsychotics, with employment rates of 30.6% versus 11.1% and employment durations of 61.3 days versus 24.7 days.[19] Our study also indicated that early clozapine initiation was associated with better employment rates in these patients. A recent retrospective cohort has concluded that late initiation of clozapine had a significantly higher risk of psychiatric rehospitalization and also showed a higher incidence of clozapine discontinuation due to physical diseases.[12] Decreased symptoms reduction in late initiators, as evidenced by our study, may lead to increased hospitalization and discontinuation.

In a retrospective cohort study conducted at London examining the records of 401 patients, it was found that each additional year of illness increased the odds of worse CGI-S (Clinical Global Impression – severity) scores by 4%. Clozapine showed the greatest benefits when started within 4 years of illness onset. This study showed that starting clozapine within 2-4 years is optimal for treatment-resistant schizophrenia20. Our study reinforced that commencing clozapine within four years of diagnosing treatment-resistant schizophrenia leads to more significant improvements than starting treatment later. However, the findings of our study are in contrast to the systematic review that failed to establish clozapine's effectiveness when started earlier in the course of illness.[13] Our findings suggest that starting clozapine earlier in the course of illness is associated with more clinical improvements.

LIMITATION OF THE STUDY

Our study had certain limitations. Since we only included clozapine naïve patients, those already on clozapine were not included hence the delay in initiation and treatment outcomes in their cases were not accounted for.Also, the study didn't explain the factors leading to delay in clozapine initiation because of its design. Another limitation was that the study was conducted in two military hospitals and that too in two neighbouring districts of KPK province, hence the sample may not be representative of the whole population.

CONCLUSION

Starting clozapine earlier in the course of illness leads to significant improvements in symptoms severity scores in treatment resistant schizophrenia. Clinicians need to start clozapine at the earliest in the eligible patients.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AUJ & SR: Data acquisition, data analysis, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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