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Delay in Clozapine Initiation in Patients with Treatment-Resistance Schizophrenia Presenting Tertiary Psychiatric Facilities

Asad Ullah Jan, Sajid Rahim*

Department of Psychiatry, Combined Military Hospital Nowshera/National University of Medical Sciences (NUMS) Pakistan,
*Department of Psychiatry, Combined Military Hospital Peshawar/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To determine the delay in Clozapine initiation in patients with treatment-resistance schizophrenia who presented to the Tertiary psychiatric facilities.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Psychiatry Combined Military Hospital, Peshawar and Department of Psychiatry Combined Military Hospital, Nowshera Pakistan, from Jan to Dec 2023.
Methodology: We recruited 103 treatment-resistant schizophrenia and Clozapine naïve patients after obtaining their consent. Patients were included by reviewing their medical history and records. The diagnosis was made by clinical interview and use of Positive and Negative syndrome scale. The data were recorded using a semi-structured questionnaire.
Results: Out of 103 patients, 78(75.7%) were male and 25(24.3%) were female. Regarding the initiation of Clozapine treatment, the mean duration from diagnosis to treatment initiation was 6.23±4.82 years. Patients were categorised based on the time to Clozapine initiation into early initiators (≤4 years), intermediate initiators (>4 years to <15 years), and delayed initiators (>15 years). The distribution across these categories was 51(49.5%) for early initiators, 47(45.6%) for intermediate initiators, and 5(4.9%) for delayed initiators.
Conclusion: There is a significant delay in Clozapine initiation despite adequate evidence to initiate it early. Clinicians should start Clozapine whenever there is a need.

Keywords: Clozapine initiation, Delay, Treatment-resistant schizophrenia

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INTRODUCTION

Treatment-resistant schizophrenia (TRS) is a challenging disorder in which numerous patients have to cope with poor outcomes and difficult social and occupational adjustments. Treatment-resistant schizophrenia is diagnosed when there is failure of two different antipsychotics with adequate trial; however, there is wide variability in the diagnosis and treatment approach. This has challenged patients' responses to treatment and their social well-being.[1] Treatment resistant schizophrenia (TRS) is characterised by persistent symptoms despite adequate trials of multiple antipsychotic medications. Nearly half of the patients diagnosed with schizophrenia respond to treatment, but there is still a large group of patients who do not respond to standard medications and continue to suffer.[2] In these treatment-resistant patients, Clozapine is indicated for symptom remission. Nonetheless, despite its efficacy and effectiveness, delays have been observed in terms of its initiation in eligible patients because of its potential side effects. Despite being the most effective intervention for TRS, the time taken to initiate Clozapine varies, and this delay can significantly impact patient outcomes.[3] Clozapine was first used in the 1960s and was subsequently withdrawn after it was linked to many deaths.[4] The medicine was reintroduced following a landmark study in 1988 that demonstrated that patients with schizophrenia who were unresponsive to other medicines showed a response to Clozapine.[5] There have been studies that have shown variability in the time taken to start Clozapine treatment. Some studies have shown that the average delay in Clozapine initiation is 5 years[6] whilst studies done in New Zealand and the UK show this delay to be 5.3 and 6.5 years respectively.[7] Other studies have shown this delay to be up to 16 years.[3] There is a dearth of data on clinical responsiveness to Clozapine after delayed initiation in treatment-resistant schizophrenia. However, the available data show that starting Clozapine with a longer delay and starting it at an older age are associated with higher Clozapine non-adherence.[8]

Correspondence: Dr Asad Ullah Jan, Department of Psychiatry, Combined Military Hospital Nowshera, Pakistan
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However, with intervention and an active approach, studies have shown that this delay has been reduced to less than 3 years.[6,9]

Pakistan is a developing country with insufficient resources for mental health services. Treatment-resistant schizophrenia is a challenge for patients and their families. It was found pertinent to look into the time delay in the initiation of Clozapine treatment for TRS to further the research on the use of Clozapine.

METHODOLOGY

The cross-sectional study was conducted at the Psychiatry Departments of CMH Peshawar and CMH Nowshera Pakistan, from January to December 2023 after obtaining approval from the Ethical Review Committee (Ref no 02 Ethical Committee/DME dated 23-01-2024). The sample size was calculated using the WHO sample size calculator, assuming an estimated proportion of early initiators of 5.2% in an earlier study.[3]

Inclusion Criteria: Clozapine naïve patients of either gender aged 18 and 50 years presenting to the Outpatient Department with a diagnosis of treatment-resistant schizophrenia with no medical or surgical comorbidities were included.

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

We enrolled 103 Clozapine naïve patients of treatment resistance schizophrenia in the study using convenient non-probability sampling after providing informed written consent. Patients fulfilling the criteria for treatment-resistant schizophrenia were included by reviewing their medical history and records. The diagnosis was made by clinical interview and the use of PANSS (Positive and Negative syndrome scale).[10] The data were recorded using a semi-structured questionnaire.

Data were collected using a semi-structured questionnaire. The data were collected after a detailed explanation and instruction regarding the research was given to the respondents. Written consent was obtained from all participants to ensure confidentiality during the entire research process. Face-to-face interviews were conducted with the patients to gather information. Demographic details and the time since the diagnosis of treatment-resistant schizophrenia were recorded by taking a detailed history of the patient, going through the treatment records, and collecting collateral information from the caregiver.

Statistical Package for Social Sciences (SPSS) version 27.0 was used for data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Analysis of variance was used to measure the difference between the means of age across the groups. Post hoc analysis was used to determine the differences in the means among the groups. The *p*-value of 0.05 or less was taken as significant.

RESULTS

This study evaluated the demographic, educational, and employment status of 103 patients, along with the age distribution and time to Clozapine initiation among different groups. The majority of the participants were male, accounting for 78(75.7%), while 25(24.3%) were female, as summarised in Table-I.

Table-I: Demographic Characteristics of the Patients (n=103)

Characteristics	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 mean age of the participants was 31.49±9.06 years. A comparison of mean ages across different groups revealed a significant difference, $p<0.001$, highlighting distinct age distributions among the groups (Table-II). Regarding the initiation of Clozapine treatment, the mean duration from diagnosis to treatment initiation was 6.23±4.82 years. Patients were categorised based on the time to Clozapine initiation into early initiators (≤4 years), intermediate initiators (>4 years but <15 years), and delayed initiators (>15 years). The distribution across these categories was 51(49.5%) for early initiators, 47(45.6%) for intermediate initiators, and 5(4.9%) for delayed initiators.

Table-II: Comparison of Age with the Time to Clozapine Initiation Groups (n=103)

Groups	Mean Age (years)	*p*-value
Early Initiators (≤4 years) (n=51)	26.59±7.83	<0.001
Intermediate Initiators(>4 years to <15 years) (n=47)	34.85±6.31	
Late Initiators(>15 years) (n=5)	50.0±0.00	

Further analysis through post-hoc tests indicated significant age differences between the early initiator group, intermediate initiator group, and late initiator group, with all comparisons yielding the *p*-value of <0.001 (Table-III).

Table-III: Inter-Group Comparison (Post Hoc Analysis)

Group Comparison	*p*-value
Group-1 vs. Group-2	<0.001
Group-2 vs. Group-3	<0.001
Group-1 vs. Group-3	<0.001

DISCUSSION

This study was conducted as a first step towards Clozapine research in Tertiary hospitals. Because there is very little work done in this field, it is believed that this study will provide an impetus to research on Clozapine use, its impact on patient outcomes, and different aspects of Clozapine use that are currently beyond the scope of this study. This study shows that a large population of patients with treatment-resistant schizophrenia continues to suffer despite the availability of effective treatment options. Nearly half of the patients included in the study were in the early initiator category, meaning that the time to Clozapine initiation was comparable to the delays elsewhere.[11] However, there was a considerable delay in Clozapine initiation in almost half of the population, and this figure does not correspond to the overall trend globally. This delay of almost 15-20 years in Clozapine initiation prolongs the duration of untreated psychosis, delays recovery, and impedes the social and occupational rehabilitation of the patients. This delay in the initiation of Clozapine in the intermediate and delayed initiator groups was comparable to the data in the Asia-Pacific region.[6] A recent multicenter cohort study conducted by Hatano *et al*. in Japan concluded that the time from schizophrenia diagnosis to Clozapine initiation was 16 years. Clozapine was initiated between 10 and 14 years after the diagnosis of schizophrenia in 21.6% of patients and within 4 years in only 5.2% of patients, whereas early (≤9 years), intermediate (10–19 years), and late (≥20 years) initiation rates were 23.9%, 38.1%, and 38.1% respectively.[3] This differs from the findings of our study, where these figures were 49.5%, 45.6%, and 4.9% in the early, intermediate, and delayed groups, respectively. Nonetheless, these figures differ in our region. A study conducted in North India showed that the mean delay in Clozapine initiation was 1.93 years.[10] However, this may not be representative of the entire population, and these figures cannot be generalised. The delay in different regions of different countries is also different, as a recent retrospective naturalistic study in the UK on 254 Clozapine-treated patients has shown that this delay is 9.81 years.[11]

Clozapine should be initiated whenever the patient fulfils the criterion for treatment-resistant schizophrenia. Evidence has emerged that there is a critical window for Clozapine initiation, inside which if it is started, the chances for improvement increase. Yashimura et al. confirmed that 2.8 years was the best predictive cut-off value of delay in initiating Clozapine for response in patients treated with Clozapine. Patients initiating Clozapine in ≤2.8 years had a response rate of 81.6% in comparison with a response rate of 30.8% (risk ratio=2.65; 95% confidence interval, 1.80, 3.63) in patients initiating it after 2.8 years of TRS diagnosis.[12] This shows that Clozapine treatment should be started within 3 years of TRS diagnosis because delay in Clozapine initiation is linked with poor treatment outcomes.[13]

Another retrospective study conducted on 401 patients in London has shown that the odds of worse outcomes increase by 4% per year of illness, and the best outcomes for Clozapine treatment were noted when it was started within 2-4 years of the start of psychotic illness. This finding indicates that a delay in Clozapine initiation can worsen treatment-resistant schizophrenia symptoms, simultaneously reducing the response to Clozapine treatment.[14] Delays in Clozapine initiation can lead to treatment resistance to Clozapine, which is associated with adverse outcomes in the form of multiple hospitalisations, poor social adjustment, and increasing suicides.[15]

Globally, there is an increasing trend in Clozapine use, and internationally, there has been a relative increase of 7.8%–197.2% over the years. Despite this steady increase, Clozapine is still underutilised, with Clozapine utilisation patterns significantly differing between countries.[16] In Asian countries, the number of patients with TRS receiving Clozapine was 18.4%.[17] This shows that Clozapine is underutilised despite its established efficacy and effectiveness.

A recent meta-analysis and systematic review has proven that Clozapine has unique benefits for patients who have not responded to first-line treatment. It has also provided evidence that using Clozapine earlier during illness as a second-line treatment option is more effective. However, this remains a subject for future research.[18]

LIMITATION OF STUDY

The study only included Clozapine naïve patients, hence those already on Clozapine were not included; hence, the delay in their cases was not considered. The study did not explain the factors leading to delay in Clozapine initiation because of its design.

CONCLUSION

There is a significant delay in Clozapine initiation despite adequate evidence to initiate it early. The delayed time to Clozapine initiation in treatment-resistant schizophrenia has wide-ranging implications, from increased patient suffering to heightened economic burden due to Clozapine resistance. Addressing this issue requires a multifaceted approach that targets barriers at the clinician, system, and patient levels. Clinicians should start Clozapine whenever there is a need. Future research should focus on identifying specific barriers at the system and individual levels that contribute to delayed initiation.

Conflict of Interest: None.

Authors' Contribution

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

AUJ & SR: Conception, study design, data acquisition, data analysis, data interpretation, drafting the manuscript, 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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