

# USE OF CLOZAPINE IN PAKISTAN: A STUDY BASED ON CLOZAPINE PATIENT MONITORING SYSTEM (CPMS)

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## ABSTRACT

Treatment options for treatment-resistant schizophrenia include clozapine, a medication often reserved for refractory cases due to its unique efficacy and potential side effects. In developing countries, no systematic data is available on Clozapine and its monitoring.

## OBJECTIVE:

The current study aimed to provide data on Clozapine monitoring.

## METHOD:

The database of Clozapine Monitoring system of Novartis Pakistan was approached and recorded medical history was analysed. Generic Clozaril was excluded from the study due to non-availability of monitoring data.

## RESULTS:

The study investigated 1256 patients from across Pakistan. The majority of the participants were male (70%). 230 mg was the average dosage of the drug during maintenance. Around 25% of the psychiatrists were prescribing the drug.

## CONCLUSION:

Clozaril is under prescribed in Pakistan and possible reasons for this underutilization of the medicine may include lack of monitoring system that comes on the top of scarcity of psychiatric services and myths about the drug and its monitoring.

## KEYWORDS:

Clozapine; Developing Countries; Pakistan; Psychiatrists; Schizophrenia; Schizophrenia, Treatment-Resistant.

## INTRODUCTION

Chronic mental illness refers to persistent and ongoing mental health conditions. These conditions can be long-term and require ongoing treatment and management. Chronic mental illness can affect daily life, relationships, and overall well-being, making it essential to seek professional help and support. With proper treatment, therapy, and support, individuals with chronic mental illness can manage their symptoms, improve their quality of life, and achieve their goals.

Treatment options for schizophrenia typically involve a combination of medications for say antipsychotics to manage symptoms like hallucinations and delusions, psychotherapy especially cognitive-behavioral therapy (CBT), family therapy, and social skills training, supportive services like case management, vocational training, and social support groups, psychosocial interventions such as rehabilitation programs, housing support, and employment assistance, lifestyle changes focusing upon regular exercise, healthy diet, stress management, and social engagement, and hospitalization to inpatient care for severe episodes or crisis situations.

Treatment-resistant schizophrenia refers to cases where symptoms persist despite adequate trials of antipsychotic medications. Therapeutic options for treatment-resistant schizophrenia may include clozapine, a medication often reserved for refractory cases, due to its unique efficacy and potential side effects.

Around one third of those suffering from this disorder develop Treatment Resistant Schizophrenia (TRS). Based on this, a conservative estimate would suggest that over 10 million people may have TRS in developing countries.<sup>1</sup> The delayed choice of Clozapine means that patients with TRS are being deprived of an effective treatment,<sup>2</sup> that increased the burden of this disease. The cost of untreated TRS in developing country is not known but it may add up to about \$34 Billion in annual direct cost in the US. Number of studies from western countries has shown that clozapine is not optimally used and there is gross underutilisation<sup>3-6</sup> as it is perceived as 'dangerous' drug.<sup>7</sup>

The mandatory Clozapine monitoring through use of 'Clozapine Patient Monitoring system' (CPMS) has provided valuable information about the pattern of Clozapine use and its side effects.<sup>8,9</sup> We aim to describe the pattern of Clozapine use by analysing the data from Clozapine Patient Monitoring System (CPMS) in Pakistan.

### METHOD

No ethical approval was required for the study, as it was anonymous data based on blood count monitoring of patients. All patients who were diagnosed with schizophrenia and taking Clozaril, and registered with the Novartis database, named Clozaril Patient Monitoring System (CPMS) were included in the study. This system of mandatory monitoring for Clozapine was started in 1992, when this medicine was introduced in Pakistan.<sup>10</sup> Although generic Clozapine brands were introduced in 2005 with a mandatory WBC monitoring policy, but this was not followed, and at the time of study, no central database was available for generic clozapine at Intercontinental Marketing Services Health Inc. (IMS)<sup>11</sup> The database of Clozaril Patient Monitoring System includes the details of diagnosis and other relevant clinical details at baseline and at subsequent blood counts, initially weekly for the first 18 weeks of treatment and then monthly until Clozapine is continued. The data were extracted based on the following variables: age & gender of patient, city of residence, duration of treatment, initial dose, final (maintenance) dose, WBC count, Neutrophil count and platelet count. All the information was entered into the SPSS version 23. Demographic statistics were computed.

### RESULTS

Between 1995 and 2012, the CPMS had a record of 1256 patients who were started on Clozapine. The majority (72%) were male. Almost all patients (n=1188, 95% of sample) belonged to four major cities of Pakistan i.e. Karachi, Lahore, Islamabad and Peshawar and almost half of these (n=539, 43%) came from one city i.e., Karachi (Table 1). There was marked change in prescribing pattern of Clozaril over time as 80% of the patients on Clozapine were registered after 2003 although Clozaril has been available since 1992.<sup>10</sup>

**Table 1**  
**Location of Clozapine Monitoring.**

Name of City	Total No of Patient n(%)	Proportion of males in sample
Hyderabad	23(1.8)	15(65.2%)
Islamabad	257(20.5)	175(68.0%)
Karachi	539(42.9)	361(66.9%)
Lahore	269(21.4)	195(72.5%)
Multan	27(2.1)	20(74.0%)
Peshawar	123(9.8)	104(84.5%)
Sukkur	18(1.4)	12(66.6%)
Total	1256(100)	882(70.2%)

**Table 2**  
**Mean dose of Clozapine and blood count.**

	Total sample	Male	Female	p-Value
Initial Clozaril dose	85.2±104	86.15±106	83.14±99	.43
Current Clozaril dose	230.2±144	236.54±146	215.52±139	.37
WBC Count	7.68±4.6	7.66±4	7.73±4	.91

**Table 3**  
**City-wise Average Initial and Maintenance Dose.**

Name of City	Mean Initial Dose	Mean Maintenance Dose
Hyderabad	275±207	413±201
Islamabad	75±58	138±93
Karachi	101±115	216±150
Lahore	25±0	313±122
Multan	252±141	286±134
Peshawar	88±92	254±102
Sukkur	132±144	227±131
Total	85±104	230±144

According to the CPMS data, only 104 out of more than 450 psychiatrists in Pakistan were registered with the system for the prescription of Clozaril.

The mean maintenance dose of Clozapine was 230±145mg (Table 2). There was significant variation in the mean dose being used in different urban centers (Table-3), with the highest dose used in Lahore (313mg±122) and Hyderabad (413mg±201), followed by Peshawar (254mg), Karachi (216mg) and Islamabad (138mg). The average maintenance dose for males was higher than female but this difference was not found to be statistically significant. The two-third of the patients were taking treatment for more than 2 years.

For the purpose of this study and for safety reasons, neutropenia is defined as a neutrophil count of 2.0 x 10<sup>9</sup>/l. Among 1256 patients, only one (0.07%) patient developed neutropenia. Besides neutropenia, other reasons for dropout includes Protocol of the drug, cost of drug, shifting to generics. Total dropout of clozapine as inferred from discussion was 21%.

### DISCUSSION

Treatment options for treatment-resistant schizophrenia may include clozapine, a medication often reserved for refractory cases, due to its unique efficacy and potential side effects. The mandatory Clozapine monitoring through use of 'Clozapine Patient Monitoring System' (CPMS) has provided valuable information about the pattern of Clozapine use and its side effects.<sup>8,9</sup> The study aimed to describe the pattern of Clozapine use by analysing the data from Clozapine Patient Monitoring System (CPMS) in Pakistan.

The major findings of this study are that less than 1300 patients have been on Clozapine in Pakistan, almost all confined to four major urban centers, and only less than one fourth of psychiatrists working in the country are involved in prescribing Clozaril. The mean dose is also quite low, i.e., 230 mg. Pakistan has a population of about 200 million and a rough estimate based on about 30% prevalence of TRS amongst those diagnosed with schizophrenia would suggest that estimated number of cases suffering from TRS in the country is 600,000. This represents a gross underutilization of an effective treatment option.

Prescribing Clozapine in a developing country is challenging. The cost and white blood cell monitoring were major barriers. The cost of Clozapine has reduced significantly since 2005, because of availability of generic brands, but this appeared to have little impact on the use of the drug.

Lack of proper information and neglecting the prescribing guidelines advice could be significant barriers to the usage of Clozapine. A study reported that Risperidone was the drug of choice for treatment-resistant cases of schizophrenia, and more than half of the prescribing sample could not tell the average recommended dose of Clozapine.<sup>12</sup>

The mean dose of Clozaril was 230+145mg. Studies reported that developing countries were using lesser average doses of the drug under discussion than the prescribed doses,<sup>13</sup> like 176 mg in Thailand.<sup>14</sup> In a study that compared the patients from a centre in Canada and South-East Asia, Chong et al found that Canadian patients were receiving higher daily doses (408 mg) than the Asian counterparts (169 mg).<sup>15</sup> Similarly, a large Chinese study found this daily dose to be around 210 mg, while 450 mg is the recommended standard of the drug.<sup>16,17</sup>

However, it is also possible that this reflects a genuinely low dose needed for response due to differences in pharmacokinetic and pharmacodynamic factors.<sup>18,19</sup> Similar differences in therapeutic dosage were also observed for other antipsychotic drugs.<sup>20,21</sup> This could be related to fact that Asians tend metabolize drug in CYP450 2D6 system more slowly and have a lower body weight.<sup>25,26</sup> However, this has not been systematically studied in case of clozapine and the evidence is limited due to small sample sizes and other methodological shortcomings.<sup>27,28</sup>

Major limitation of the study is that it describes the situation of clozapine prescription for only one major brand and is based on the cross-sectional data provided by Novartis. However, according to the IMS data,<sup>11</sup> the generic Clozapine has only 3% of the total market share of antipsychotic in Pakistan.

This study has major implications for training, practice and guidelines development. Although inadequate use of Clozapine is documented, we are not aware of a study which shows that almost two third of psychiatrists in a large country, do not prescribe the drug at all. Such a use dose may result from inadequate knowledge about the use of Clozapine or its perception as a 'dangerous' drug.<sup>7</sup> This needs to address in training and educational development of psychiatrists in developing countries.

## CONCLUSION

It can be concluded that proportion of patients using clozapine and the number of psychiatrists prescribing the treatment of first choice in TRS is grossly inadequate. The mean dose being used is also low but this may be a reflection of genuinely low dose needed for a developing country setting.

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## CONFLICT OF INTEREST

None

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None

## DISCLOSURE

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**AUTHOR(S) CONTRIBUTION / UNDERTAKING FORM**

Sr. #	Author(s) Name	Author(s) Affiliation	Contribution
<b>1.</b>	Raza ur Rahman	Faculty of Health & Medical Sciences, Hamdard University, Karachi, Pakistan.	Acquired the data from Novartis and wrote the draft.
<b>2.</b>	Saeed Farooq	Global Research, National Institute of Health and Care Research, UK; Psychiatry and Public Mental Health, School of Medicine, Keele University, UK.	Wrote the draft.

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