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## **SHORT COMMUNICATION:**

**CLOZAPINE MONITORING THROUGH PATIENTS MONITORING SYSTEM (CPMS)** 

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#### **ABSTRACT**

## **INTRODUCTION**

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. Current study aimed to provide data on Clozapine monitoring

#### **METHOD**

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

#### **RESULTS**

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

## **CONCLUSION**

The study concludes that medical students, specifically in final professional year of study, report high 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.

#### **KEY WORDS**

Prescribing pattern, Low dose Clozaril, Pakistan

### **INTRODUCTION**

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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. 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.

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>.

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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**

All the patients who were diagnosed with schizophrenia, were taking Clozaril and were registered to Novartis data base 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. Although generic Clozapine brands were introduced in 2005 with mandatory WBC monitoring policy but this was not followed and at present no central data base is available for generic clozapine at IMS<sup>11</sup>. The data base of Clozaril Patient Monitoring System, includes the detais of diagnosis and other relevant clinical details at baseline and at subsequently blood counts initially weekly for first 18 weeks of treatment and then monthly until Clozapine is continued. The data was extracted on 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 to 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	Proportion of male in
	n (%)	sample

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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 <u>+</u> 104	86.15 <u>+</u> 106	83.14 <u>+</u> 99	.43
Current Clozaril dose	230.2 <u>+</u> 144	236.54 <u>+</u> 146	215.52 <u>+</u> 139	.37
WBC Count	7.68 <u>+</u> 4.6	7.66 <u>+</u> 4	7.73 <u>+</u> 4	.91

Table-3 City wise average initial and maintenance dose

Name of City	Initial dose mean	Maintenance dose mean
Hyderabad	275 <u>+</u> 207	413 <u>+</u> 201
Islamabad	75 <u>+</u> 58	138 <u>+</u> 93
Karachi	101 <u>+</u> 115	216 <u>+</u> 150
Lahore	25 <u>+</u> 0	313 <u>+122</u>

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Multan	252 <u>+</u> 141	286 <u>+</u> 134
Peshawar	88 <u>+</u> 92	254 <u>+</u> 102
Sukkur	132 <u>+</u> 144	227 <u>+</u> 131
Total	85 <u>+</u> 104	230 <u>+</u> 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). The highest dose was being used in Lahore (313mg±122) and Hyderabad (413mg±201) followed by Peshawar (254mg), Karachi (216mg) and Islamabad (138mg). The average maintenance dose for male 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  $2.0 \times 10^9$ /l. Among 1256 patients only one (0.07%) patient develop neutropenia. Besides neutropenia other reason for dropout includes Protocol of the drug, cost of drug, shifting to generics. Total drop out of clozapine as inferred from discussion is 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.

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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 are major barriers. The Cost of Clozapine has reduced significantly since 2005, due to availability of generic brands but this appeared to have little impact on the use of drug.

Lack of proper information and neglecting the prescribing guidelines advice could be significant barriers to use 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 Singapore, Chong et al (2010) found that Canadian patients were receiving higher daily doses (450 mg) than the Asian counter parts (169 mg). Similarly, a large Chinese study found this daily dose to be around 210 mg (Tian Mei Si et al 2006), while 450 mg is the recommended standard of the drug<sup>15-17</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</sup>, <sup>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>.

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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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