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BARRIERS TO CLOZAPINE USE IN TREATMENT-REFRACTORY POPULATION IN KARACHI, PAKISTAN.

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ABSTRACT

OBJECTIVE
To investigate the causes accountable for serving as barriers in prescribing clozapine in several outpatient departments in Karachi, Pakistan.

STUDY DESIGN
A cross-sectional study

PLACE AND DURATION OF THE STUDY
Psychiatrist and residents conducting clinics in Karachi from May to July 2022.

METHOD
This study conducted over three months using a structured questionnaire from 105 physicians with previous formal training in psychiatry. Statistical analysis was done using the Chi-Square test of association.

RESULTS
Out of 105 doctors offering psychiatric services at various locations, 70% mentioned that they were uncomfortable prescribing clozapine earlier in the course, with its adverse effects profile being the most popular reason for its avoidance by the patients and/or their families. Clozapine's availability and its cost were also common barriers to prescribing clozapine. Most doctors agreed that they would have felt more comfortable if they had had some clozapine training and attended clozapine clinics during their training.

CONCLUSION
The anticipation of medication nonadherence and monitoring requirements coupled with overestimating the adverse effect profile stems from inadequate experience with the drug. Steps should be taken by the graduate medical education at the training hospitals to organise clozapine clinics and offer clozapine training to promote the use of this effective drug to improve the prognosis and function suffering from this debilitating illness.

KEYWORDS
Agranulocytosis; Clozapine; Education, Medical, Graduate; Medication Adherence; Mental Health Services; Prescriptions.

INTRODUCTION
Associated with significant disability, the epitome of mental illness known as schizophrenia affects around 0.32% of the population worldwide.[1] As per the evidence, schizophrenia affects individuals and their families, both socially and economically, and ultimately affects the quality of life of an individual.[2] The exact prevalence of schizophrenia in Pakistan is currently unknown, which makes this debilitating illness more challenging to manage.

The risk of agranulocytosis is the primary reason clozapine patients must undergo regular absolute neutrophil count (ANC) monitoring, which in the United States is monitored by the Risk Evaluation and Mitigation Strategy (REMS). It is important to note that agranulocytosis is relatively rare in clinical practice due to the revised prescribing protocols and guidelines.[3] There is growing evidence that clozapine can be safely used with minimal adverse effects, if closely monitored.[4] Blackman et al[5] observed no notable difference in cell counts compared to baseline after 12 weeks of clozapine initiation. Despite the overwhelming need for clozapine monitoring, multiple patient surveys found patients' satisfaction to be high with continuing clozapine treatment.[6] Although agranulocytosis, clozapine-induced intestinal hypomotility, and bowel obstruction may result in clozapine-related death,[7] the unique clozapine efficacy has still gained global preference for clozapine over all other antipsychotic medications, including first-generation[8,9] as well as second-generation antipsychotic drugs.[10] Protocols and guidelines regarding clozapine dosing and indication criteria, when not adhered to, lead to delaying of initiation of clozapine by an average of 5 years[11] and 8.9 years in males.[12] Sadly, a large population of patients with treatment-resistant schizophrenia (TRS) receives antipsychotic polypharmacy with limited benefits,[13] worsening the prognosis and increasing the risk of adverse effects.[14]

One of the most significant barriers to prescribing clozapine is the fear of adverse effects and mandatory blood monitoring.[4] The global data show under-prescription, low-dosing, and delay in initiating clozapine treatment. Unfortunately, specific reasons behind the infrequent and suboptimal use of

clozapine in Pakistan are unknown. This study attempts to identify the obstacles to prescribing/utilising clozapine in patients with TRS to find solutions to overcome these barriers.

METHOD

Study Design and Sampling

This cross-sectional study was conducted using a non-probability convenience sampling technique from psychiatrists currently practicing in the densely populated city of Karachi, Pakistan, from May 2022 to July 2022.

Ethical Consideration

Ethical approval was obtained from the review committee of the District Health Officer (DHO) Karachi (South).

The following were the Eligibility Criteria:

Inclusion Criteria

1. Qualified psychiatrists working in Government and Private hospitals and private clinics.
   - MCPS: Member of the College of Physicians and Surgeons Pakistan
   - FCPS: Fellow of College of Physicians and Surgeons Pakistan
2. Non-Qualified Physicians (Chief residents in Psychiatry programs) conducting private psychiatric outpatient departments.
   - Chief Residents

Exclusion Criteria

1. Physicians with no formal training in Psychiatry.
2. Psychiatrists and other residents refused to consent to the study.
3. Individuals who provided incomplete questionnaires.

Data Collection and Questionnaire

A total sample of 105 was collected from psychiatrists and residents conducting clinics in Karachi, and a structured questionnaire was used to get information on the knowledge and prescribing trends of clozapine.

Responses to the questionnaire were finalized after a pilot study done on thirty (30) doctors and comprised of questions related to their demographics, education level, reasons behind avoiding the prescription of clozapine, healthcare barriers, and any previous training targeted to help them equip with knowledge on using this drug.

Although the primary language used to construct the questionnaire was English, it was translated into the local language (Urdu) for a better understanding of the questions for the participants. Cronbach's alpha to check the reliability of the questionnaire was 0.685. Informed consent was obtained from all the participants to include their responses in the study while maintaining anonymity.

An informed consent form was attached to the questionnaire, which informed all the potential participants about the purpose of data collection and incorporating these findings in the study while maintaining anonymity. The questionnaire was anonymous and guaranteed the confidentiality of the study participants as it did not document any information that could link individuals to the study.

Statistical Analysis

Data entry and statistical analysis were done using Statistical Package for Social Sciences 25.0 (SPSS v25.0). Percentages/Frequency of responses were calculated for relevant variables. Chi-squared test of association was used. The significance level was $p < 0.05$.

RESULTS

A total of 105 mental health providers in different clinical settings across the city were requested to fill out a questionnaire. As evident from Table 1, the majority of the physicians providing mental health care were chief residents in residency programs, while 43.8% were qualified psychiatrists. Surprisingly 70% of the doctors had mentioned that they were not comfortable prescribing clozapine, with healthcare issues being the most common reason for 88.6% of providers not prescribing it. Following complex protocols along with the availability of the drug was found to be the most common healthcare issue serving as a barrier for clozapine to be prescribed (61.0%). However, lack of resources and expenses to monitor clozapine levels and frequently repeated blood counts was the main issue highlighted by 24.8% of the doctors when prescribing clozapine.

Almost 11.4% of the doctors stated that patients and families of those patients refused to take the drug, and that was another common reason for clozapine to be excluded from the prescription. About 92.4% of the respondents highlighted that the side effect profile was the most common reason for a patient or family to refuse the drug. However, 6.7% of the physicians voted for repeated blood samples to be the cause of denying clozapine. It was astonishing to see that 75% of the doctors had not received any formal training for clozapine, and none of them had clozapine clinics at their respective residency programs.

Table 1

Descriptive analysis and frequencies of variables in the study.

		Frequencies	
Variables		**Total (n=105)**	**Percentage**
Qualifications	MCPS*	21	20%
	FCPS*	25	23.8%
	Others (Senior Residents, chief residents)	59	56.2%
Clinical Setup	Private Practice	62	59%
	Government Hospital	42	40%
	Private hospitals	1	1%
Preferred first-line treatment for schizophrenia	Risperidone	49	46.7%
	Haloperidol	56	53.3%
Comfortable in Prescribing clozapine	No	74	70.5%
	Yes	31	29.5%
Reasons for patients refusing clozapine prescription	Side effect Scare	97	92.4%
	Repeated Blood samples	7	6.7%
	Unable to tolerate clozapine after taking a few doses	1	1%
Is side effect profile the biggest concern when prescribing clozapine?	Yes	100	100%
	No	0	0
	Maybe	0	0
Reasons to not prescribe clozapine other than Side-effect profile	Healthcare-related issues (Availability, Cost, etc.)	93	88.6%
	Patient or family refusal	12	11.4%
Most Common Healthcare issues in prescribing clozapine	Complex Protocols and drug availability	64	61.0%
	Unable to monitor clozapine levels and repeated blood counts (Lack of resources and expenses)	26	24.8%
	Expensive medication	15	14.3
When is clozapine generally prescribed?	Treatment-resistant cases	105	100%
Are any specific courses attended related to clozapine?	Yes	26	24.8%
	No Specific Training	79	75.2%
Have you attended clozapine clinics during training?	No Clozapine clinics were available	105	100%
Maintenance of Patient records	No patient records Stored	85	81.0%
	Maintained patient records on paper files	19	18.1%
	Maintained paper records on E-Media	1	1.0%

Note: *MCPS: Member of the College of Physicians and Surgeons Pakistan; *FCPS: Fellow of College of Physicians and Surgeons Pakistan

After a pilot study, we found that the most common medications initiated on the diagnosis of schizophrenia were risperidone (46.6%) and Haloperidol (53.3%), with risperidone being a popular choice in private practices because of better affordability. Haloperidol was seen to be more in numbers at the government hospitals(p<0.001).

Table 2

First-line treatment offered at different clinical setups.

		First line Treatment for Schizophernia			
		Riapweisone	Haloperidol	Total	P-value
Clinical Setup	**Private Practice**	**43**	**19**	**62**	**<0.001**
	% Within Clinical Setup	**69.4%**	**30.6%**	**100.0%**	
	Government Hospital	**5**	**37**	**42**	
	% Within Clinical Setup	**11.9%**	**88.1%**	**100.0%**	
	Private Hospital	**1**	**0**	**1**	
	% Within Clinical Setup	**100.0%**	**0.0%**	**100.0%**	
Total		**49**	**56**	**105**	
% Within Clinical Setup		**46.6%**	**53.3%**	**100.0%**	

Out of the total sample size, 75% (n=79) did not receive any specific training related to clozapine. Further analysis showed a positive correlation with being comfortable prescribing the drug. Out of 79 providers who did not receive any particular training or did not take any specific course for clozapine, 93.6% (n=74) responded with not being comfortable prescribing it.

However, out of the total 26 doctors who received training or attended courses on clozapine, all were comfortable prescribing clozapine(p<0.001).

Table 3

Cross tabulation of comfort when prescribing clozapine and any specific courses taken.

		Attended any clozapine-specific courses			
		No specific training	Yes	Total	P-value
Comfortable in prescribing clozapine	**No**	**74**	**0**	**74**	**<0.001**
	% Within Comfortable in Prescribing	**100.0%**	**0.0%**	**100.0%**	
	Yes	**5**	**26**	**31**	
	% Within Comfortable in Prescribing	**16.1%**	**83.9%**	**100.0%**	
Total		**79**	**26**	**105**	
% Within Comfortable in Prescribing		**75.2%**	**24.8%**	**100.0%**	

Interestingly, healthcare issues were diverse across multiple clinical settings. Of the 62 private practices, all mentioned complex protocols and drug availability as the most common cause. However, 26 doctors (61.9%) working at government hospitals voted the inability to monitor clozapine levels and blood counts repeatedly as a common cause due to financial issues of the patients.

Another issue highlighted at the government hospitals was the patients, in many instances, could not afford medications when free medications at these sites were not available, which also served as a significant hurdle for the doctors (35.7%) to prescribe clozapine to the patients(p<0.001).

Table 4

Healthcare-related issues according to clinical setup serving as barriers to prescribing clozapine.

		Healthcare related issues				
		Complex Protocols and drug avilability	Unable to monitor clozapine levels and repeated blood counts	Expensive Medication	Total	P-value
Clinical Setup	Private practice	62	0	0	62	<0.001
	% Within Clinical Setup	100.0%	0.0%	0.0%	100.0%	
	Government Hospital	1	26	15	42	
	% Within Clinical Setup	2.4%	61.9%	35.7%	100.0%	
	Private hospitals	1	0	0	1	
	% Within Clinical Setup	100.0%	0.0%	0.0%	100.0%	
Total		64	26	15	105	
% Within Clinical Setup		61.0%	24.8%	14.3%	100.0%	

Literature suggests that clozapine has satisfactory results if started earlier in the course.[11,12] After the bone marrow toxicity scare in 1975, this has continued to interfere with practice in developing countries like Pakistan. During the treatment, clozapine levels need to be monitored along with the blood counts to look for agranulocytosis. Other than this, the patient's metabolic profile needs to be seen and monitored regularly. Everything related to the treatment needs to be on record, which might help a physician decide. On inquiring if they had maintained patient records, 19 out of the 62 providers (30.6%) had maintained records in private practice while previous health records in government hospitals were not maintained.

Table 5

Maintaining health records in various clinical setups.

		Maintaining Patient Health Records				
		No Records Stored	Maintained patient record on paper fiels	Maintained patient records on E-media	Total	P-value
Clinical Setup	Private Practice	43	19	0	62	<0.001
	% Within Clinical Setup	69.4%	30.6%	0.0%	100.0%	
	Government Hospital	42	0	0	42	
	% Within Clinical Setup	100.0%	0.0%	0.0%	100.0%	
	Private Hospitals	0	0	1	1	
	% Within Clinical Setup	0.0%	0.0%	100.0%	100.0%	
Total		85	19	1	105	
% Within Clinical Setup		81.0%	18.1%	1.0%	100.0%	

DISCUSSION

Although the under-prescription of antipsychotics is rarely a problem in this part of the world, clozapine continues to break this stereotype and remains one of the most underutilised drugs in Karachi, Pakistan, where mental health and psychiatry have only recently gained importance. The lack of mental health providers coupled with the increased burden of mental disorders highlights the need for and importance of adequate care to be provided to reduce the disease burden. Our finding that 70.5% of physicians surveyed in this study were uncomfortable prescribing clozapine is consistent with previous studies in other parts of the world.[15,16] Although adverse effect profiles can be monitored and the drug can be safely prescribed, 92.4% of the physicians surveyed in this study mentioned that adverse effects were the main reason for patients and their families to refuse clozapine prescriptions. This finding was supported by the results from a nationwide study by Moody and Eatmon,[17] which reported that adverse effects were the most encountered hurdle to prescribing clozapine, along with blood monitoring and lack of training and experience in prescribing the drug. Our study also revealed that the need for repeated blood counts was another reason for clozapine refusal by the patients and their families. Approximately 62% of the surveyed physicians reported that patients presenting to government hospitals could not afford the repeated blood tests, “In addition, most patients do not have any medical insurance to cover for their treatments.”

while others within the same category would consider it a hassle to go to the hospital or lab repeatedly. As evident by studies reporting clozapine barriers,[18,19] patient nonadherence and refusal of blood work were among the common reasons for initiating clozapine treatment.

However, the study found multiple other factors responsible for the under-prescription of clozapine besides adverse effects. Various healthcare issues were also recognised as one of the most common barriers when prescribing clozapine. Drug availability and complex blood monitoring protocols are the most common healthcare issue. A series of responses by the respondents showed that clozapine was not always available to be dispensed in pharmacies, mainly in the government sectors where most patients cannot afford clozapine-related costs, such as the implementation of protocols to be followed to monitor clozapine's toxicity and adverse effects. Clozapine initiation protocols include a slow increase in clozapine dose over 2-3 weeks, and maintaining a plasma level of at least 350 µg/L for an adequate trial is mandatory to avoid adverse effects and dose adjustments according to the needs of the patient.[20] Even if dose titration can be effectively managed along with regular blood monitoring, assessment of clozapine levels can be extremely expensive and not affordable for most patients in Pakistan. Although the metabolic side effects are much more common,

it is primarily the risk of agranulocytosis in only approximately 1% of the patient population,[21] preventing mental health providers from prescribing clozapine. The prescribers are wary of the adverse effects and anticipate poor patient adherence to clozapine and monitoring requirements. These factors may also explain psychiatrists' lack of training in prescribing clozapine. In our study, out of 105 physicians surveyed, 70.4% (n=74) did not receive any clozapine-specific training and responded as uncomfortable prescribing it. Prior exposure to clozapine training showed a linear relationship with being comfortable in prescribing clozapine. Unfortunately, 93.6% of the surveyed providers who did not have any clozapine training were not comfortable prescribing clozapine. On the contrary, clozapine-trained physicians had no problems prescribing clozapine. These findings are consistent with a study conducted on physician residents in the United States, where a vast majority were uncomfortable prescribing clozapine due to a lack of experience and training.[22] This lack of clozapine training has been related to under prescription of clozapine by other studies in the past as well.[6,23]

Another unforeseen obstacle to clozapine use is the lack of maintaining medical records, such as adverse effects and results from frequent blood work, which is crucial for the safe and effective use of clozapine treatment. Unfortunately, most surveyed physicians (i.e., 81%) did not maintain any patients' medical records at their clinics, which further increased concerns about clozapine safety.

Although a tedious process requiring resources, clozapine training should be mandated during psychiatry residency to help equip future mental health providers with tools to confidently prescribe clozapine and educate patients and their families on clozapine's efficacy in the treatment-refractory patient population. Healthcare systems in Pakistan should provide financial and personnel resources in setting up clozapine clinics where properly trained physicians can make clozapine readily available and free-of-cost blood monitoring can be offered.

Limitations

The results from this study are based on a cross-sectional survey using a questionnaire specifically developed for this study and should be interpreted with caution. Other limitations are as follows:

I. Mental health providers fill out the responses in the questionnaire based on their memory, which is subject to recall bias.
ii. Due to the lack of qualified psychiatrists in the Karachi our sample size was limited to 105.
iii. There can be a possibility that many providers might not have fully disclosed the prescribing trend and emphasized one aspect of healthcare issues, and hence there might be heavy utilization of subjected reported views.
iv. Many doctors included in the survey were currently enrolled in the same residency program and might have similar prescribing trends and may encounter similar barriers when prescribing clozapine.
v. Our study outlines the prescribing practices in Karachi, Pakistan, where the number of qualified psychiatrists is low. Thus, the results cannot be generalized compared to places with more qualified psychiatrists.

CONCLUSION

Despite associated risks, clozapine has shown enough clinical evidence to be seriously considered in managing the treatment-refractory population. In a country like Pakistan with limited resources, future investments in effective treatment of the schizophrenia population can eventually be cost-effective and improve long-term outcomes. This can be achieved through promoting clozapine training during psychiatry residencies and setting up clozapine clinics where clozapine is freely available to facilitate safe and effective use of clozapine, requiring maintenance of medical records on adverse effects and results from blood monitoring.

DECLARATION OF INTEREST

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REFERENCES

1. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. Schizophr Bull. 2018;44(6):1195-1203. doi:10.1093/schbul/sby058
2. Health care reform for Americans with severe mental illnesses: report of the National Advisory Mental Health Council. Am J Psychiatry. 1993;150(10):1447-1465. doi:10.1176/ajp.150.10.1447
3. Bishara D, Taylor D. Adverse effects of clozapine in older patients: epidemiology, prevention and management. Drugs Aging. 2014;31(1):11-20. doi:10.1007/s40266-013-0144-2
4. Shah P, Iwata Y, Plitman E, et al. The impact of delay in clozapine initiation on treatment outcomes in patients with treatment-resistant schizophrenia: A systematic review. Psychiatry Res. 2018;268:114-122. doi:10.1016/j.psychres.2018.06.070
5. Blackman G, Lisshammar JEL, Zafar R, et al. Clozapine Response in Schizophrenia and Hematological Changes. J Clin Psychopharmacol. 2021;41(1):19-24. doi:10.1097/JCP.0000000000001329
6. Rubio JM, Kane JM. How and when to use clozapine. Acta Psychiatr Scand. 2020;141(3):178-189. doi:10.1111/acps.13111

7. Every-Palmer S, Ellis PM. Clozapine-Induced Gastrointestinal Hypomotility: A 22-Year Bi-National Pharmacovigilance Study of Serious or Fatal 'Slow Gut' Reactions, and Comparison with International Drug Safety Advice. CNS Drugs. 2017;31(8):699-709. doi:10.1007/s40263-017-0448-6
8. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry. 1999;156(7):990-999. doi:10.1176/ajp.156.7.990
9. Samara MT, Dold M, Gianatsi M, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. JAMA Psychiatry. 2016;73(3):199-210. doi:10.1001/jamapsychiatry.2015.2955
10. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006;63(10):1079-1087. doi:10.1001/archpsyc.63.10.1079
11. Nielsen J, Røge R, Schjerning O, Sørensen HJ, Taylor D. Geographical and temporal variations in clozapine prescription for schizophrenia. Eur Neuropsychopharmacol. 2012;22(11):818-824. doi:10.1016/j.euroneuro.2012.03.003
12. Trinczek E, Heinzel-Gutenbrunner M, Haberhausen M, Bachmann CJ. Time to Initiation of Clozapine Treatment in Children and Adolescents with Early-Onset Schizophrenia. Pharmacopsychiatry. 2016;49(6):254-259. doi:10.1055/s-0042-116947
13. Wheeler AJ. Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. Ann Pharmacother. 2008;42(6):852-860. doi:10.1345/aph.1K662
14. Üçok A, Çikrikçili U, Karabulut S, et al. Delayed initiation of clozapine may be related to poor response in treatment-resistant schizophrenia. Int Clin Psychopharmacol. 2015;30(5):290-295. doi:10.1097/YIC.0000000000000086
15. Schulte PFJ, Bogers J, Bond-Veerman SRT, Cohen D. Moving forward with clozapine. Acta Psychiatr Scand. 2020;142(2):75-77. doi:10.1111/acps.13224
16. Shad MU, Felzien E, Roy K, Sethi S. How to identify and manage non-response to clozapine?. Asian J Psychiatr. 2019;45:50-52. doi:10.1016/j.ajp.2019.08.016
17. Moody BL, Eatmon CV. Perceived Barriers and Facilitators of Clozapine Use: A National Survey of Veterans Affairs Prescribers. Fed Pract. 2019;36(Suppl 6):S22-S27.
18. Farooq S, Choudry A, Cohen D, Naeem F, Ayub M. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. BJPsych Bull. 2019;43(1):8-16. doi:10.1192/bjb.2018.67
19. Ismail D, Tounsi K, Zolezzi M, Eltorki Y. A qualitative exploration of clozapine prescribing and monitoring practices in the Arabian Gulf countries. Asian J Psychiatr. 2019;39:93-97. doi:10.1016/j.ajp.2018.12.011
20. Schizophrenia and related psychoses. In: The Maudsley Prescribing Guidelines in Psychiatry. 13th ed.Wiley Blackwell; 2018. p. 156–7. Available from:https://dl.uswr.ac.ir/bitstream/Hannan/32636/1/9781119442608.pdf
21. Atkin K, Kendall F, Gould D, Freeman H, Liberman J, O'Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. Br J Psychiatry. 1996;169(4):483-488. doi:10.1192/bjp.169.4.483
22. Singh B, Hughes AJ, Roerig JL. Comfort Level and Barriers to the Appropriate Use of Clozapine: a Preliminary Survey of US Psychiatric Residents. Acad Psychiatry. 2020;44(1):53-58. doi:10.1007/s40596-019-01134-7
23. Verdoux H, Quiles C, Bachmann CJ, Siskind D. Prescriber and institutional barriers and facilitators of clozapine use: A systematic review. Schizophr Res. 2018;201:10-19. doi:10.1016/j.schres.2018.05.046

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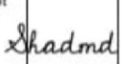
1.	Mujeeb U. Shad	University of Nevada, Las Vegas, USA	Manuscript Author	
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