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Original Research Article

A Cross-Sectional Survey of Clozapine Prescribing Trends Among Psychiatrists in India

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Abstract:

Background: Clozapine has been found to be an effective atypical antipsychotic since the time of discovery. Clozapine was also approved by FDA for reducing the risk of suicide in schizophrenic or schizoaffective patients judged to be at chronic risk for suicidal behavior in December 2002. There is a scarcity of data from the Indian subcontinent on the preference of clozapine in the medico-surgical setting.

Aims and Objective: To study the clozapine prescribing trends in various psychiatric disorders among psychiatrists in India.

Methods: A survey using structured questionnaire form was done with 125 psychiatrists which included various aspects like area of practice, starting dose of clozapine, maximum dose of clozapine tried, most common side effects encountered during practice, preference of using clozapine in various disorders, monitoring side effects, most common augmentation agents, etc.

Results: Majority psychiatrists have had good experience using clozapine. However, side effects and need for repeated blood investigations turned out to be a barrier for its use.

Conclusion: Need to influence policy to ensure wider availability of blood investigations to ensure increased usage of clozapine while keeping it in safety checks.

Introduction

Clozapine has been found to be an effective atypical antipsychotic since the time of discovery. However, it was withdrawn from the market in 1976 as there were many reports of fatal agranulocytosis as one of the side effects. [1]

However, enthusiasm for the drug was maintained by a small cadre of clinical investigators including G. Honigfeld at Sandoz, who observed that clozapine, was remarkably effective in treatment-resistant patients. This led to a landmark double-blind study of clozapine in a well-defined group of treatment-resistant patients whose blood cell counts were closely monitored during treatment and ultimately to its introduction to the US market in 1990.[2] Clozapine was approved by the FDA in 1990.Clozapine was also approved for reducing the risk of suicide in schizophrenic or schizoaffective patients judged to be at chronic risk for suicidal behavior in December 2002. [3]

Studies later on showed its effectiveness in treatment-resistant schizophrenia, suicide prevention & low propensity for extra pyramidal symptoms when compared to other antipsychotics and hence paved the way for its reintroduction. [4,5]

It has also been found that patients on clozapine had lower discontinuation rates, were less likely to need to switch antipsychotics or polypharmacy and had decreased relapse rates.[6,7] The only aspect to be kept in mind in these individuals is regular monitoring of blood parameters for a granulocytosis.[8] Current clinical practice guidelines define treatment-resistant schizophrenia as failure to respond to adequate trials with two unrelated antipsychotics (at least 1 of which should be a non-clozapine second-generation antipsychotic such as risperidone, olanzapine, or quetiapine).[9–11]

The need for regular blood tests and distressing side effects such as excessive sedation hyper salivation, metabolic syndrome and rarely, risk of myocarditis and cardiomyopathy has been a major concern while prescribing, which in-turn has led to underutilization of this drug.[12] Despite clear guidelines, and proven cost-effectiveness, prescribing of clozapine in treatment-resistant

schizophrenia seems to remain something of a postcode lottery.

There is a scarcity of data from the Indian subcontinent on the preference of clozapine in the medico-surgical setting. In this context, the current study aims at analyzing the pattern of use of clozapine among various psychiatrists.

Materials and Methods

Data was collected using purposive sampling strategy whereby a survey using structured questionnaire form was done**,** which included various aspects like area of practice, starting dose of clozapine, maximum dose of clozapine tried, most common side effects encountered during practice, preference of using clozapine in various disorders, monitoring side effects, most common augmentation agents, etc.

The form was then sent to various psychiatrists practising in India using different social media platforms by which a response of a 100 practicing psychiatrists were accrued over a period of 1 year.

Psychiatrists who were not willing to participate were not included in the study. Apart from that psychiatrists with no prior expertise of using clozapine in clinical practice or psychiatrists who were currently involved in research and development of clozapine or associated with any pharmaceutical company actively conducting trials on clozapine were excluded. Keeping their names confidential and responses were collected, documented, tabulated in a proper format, and studied to evaluate the clinicians' attitude towards clozapine.

Results

A total of 125 psychiatrists took part in the study and on assessment of the area of practicing the psychiatrists who participated in the study, it was observed that most psychiatrist belonged to Madhya Pradesh while almost equal number belonged to Delhi & NCR, Rajasthan, and Uttar Pradesh. The highest number of psychiatrists practised in Medical colleges followed by private clinics/corporate hospitals.

Table 1: Years of practising

Years of practising	Freq (N=125)	Percentage (%)
<1	15	12
2-5	57	45.6
6-9	34	27.2
>10	19	15.2

Table 1shows that most psychiatrists had experience of about 2-5 years followed by psychiatrists having 6-9 years of cumulative experience. About three-fourths of psychiatrists who participated in the history were early career psychiatrists, that is, had less than 5 years of experience.

Table 2: Various parameters associated with use of Clozapine by different psychiatrists.

Using clozapine to manage acute suicidality	Freq (N=125)	Percentage (%)
Yes	42	33.6
No	83	66.4
Delay in usage of clozapine		
Side effects/ metabolic issues	47	37.6
Difficulty in investigations	28	22.4
Difficulty in ensuring compliance	13	10.4
Difficulty in titrating the dose	9	7.2
Delayed/ unconfirmed diagnosis	4	3.2
Not providing consent	2	1.6
Others	11	8.8
No delay	11	8.8
Frequency of ordering TLC / CBC		
Monthly	62	49.6
Weekly	39	31.2
SOS basis (if patient develops side effects	21	16.8
Only baseline	3	2.4
Most common side effect seen with clozapine		
Excess salivation	55	44
Sedation	49	39.2
Weight gain	12	9.6
Constipation	9	7.2
Maximum dose of clozapine tried (in mg)		
Upto 400	68	54.4
400-600	38	30.4

600-800	14	11.2
>800	5	4
Is clozapine underutilized in India?		
Yes	87	69.6
No	38	30.4
Overall experience with clozapine in psychosis		
Excellent	24	19.2
Good	79	63.2
Average	20	16
Bad	1	0.8
Poor	1	0.8

The survey had an unequivocal response from psychiatrists as almost all psychiatrists opined that they do not use it for its anit-suicidal properties. As shown in table 2 assessment of causes of delay in usage of clozapine in cases shows that the overwhelming number of side effects associated with clozapine came out to be top reason for delay in usage of clozapine by psychiatrists. This was coupled with difficulty in investigations by the patients or their care givers.

Table 2also depicts the frequency of ordering blood investigation CBC. About half of the psychiatrists order Complete blood count on monthly basis followed by weekly basis and then SOS, that is, if the patient develops side effects. As depicted in the table the most common side effects associated with clozapine; excess salivation and sedation were the 2 top side effects reported on the use of clozapine in patients.

It also shows the maximum dose of clozapine tried by the psychiatrists. A whooping half number of psychiatrists tried the doses upto400 mg followed by 400-600 mg in their clinical practice. Only 4 % of psychiatrists reported having used clozapine in doses 800 and above.

On evaluation of the opinion of psychiatrists who participated in the study as to whether clozapine is underutilised in India. Three-fourth of the participating sample believed that clozapine is being underutilised in the country while the remaining one-fourth believed otherwise. About 80% of the participating psychiatrists had good or excellent experience using clozapine.

Discussion

This study was done using an online based survey form and about a hundred psychiatrists participated in this study after providing appropriate consent for the same.

Most psychiatrists in the study were from Madhya Pradesh, followed by Delhi & NCR, Rajasthan, and Uttar Pradesh. This suggests that clozapine is being used in a relatively wide geographic area of India.
Most psychiatrists practiced in medical colleges, followed by private clinics/corporate hospitals. This suggests that clozapine is being used in both academic and community settings. Most psychiatrists had 2-5 years of experience, followed by those with 6-9 years of experience. About 75% of psychiatrists were early career psychiatrists. This suggests that clozapine is being used by psychiatrists of all levels of experience. Almost one thirdof psychiatrists did not use clozapine for its anti-suicidal properties. This is surprising, given that clozapine is one of the most effective treatments for suicidality in schizophrenia. It is possible that psychiatrists are not aware of clozapine's anti-suicidal effects, or that they are hesitant to use it for this purpose due to its side effects.

The most common reason for delay in clozapine use was the overwhelming number of side effects associated with the drug, coupled with difficulty in investigations by patients or their caregivers. This is a major barrier to clozapine use in India, and it highlights the need for education and support for patients and their caregivers.

About half of the psychiatrists ordered complete blood count (CBC) only on an monthly basis. It is possible that psychiatrists are hesitant to order blood tests more frequently due to the cost or the inconvenience for patients. Excess salivation and sedation were the two most common side effects reported with clozapine use. These side effects can be severe and debilitating, and they can contribute to the delay in clozapine initiation and adherence.

Three-fourths of psychiatrists believed that clozapine was being underutilized in India, while the remaining one-fourth believed otherwise. This suggests that there is a range of opinions on the issue of clozapine underutilization among Indian psychiatrists.

Half of the psychiatrists tried clozapine doses of up to 400 mg in their clinical practice, while only 4% reported using doses of 800 mg or higher. This suggests that psychiatrists are generally cautious about using high doses of clozapine, likely due to concerns about side effects.

About 80% of the participating psychiatrists had good or excellent experience using clozapine. This suggests that clozapine is an effective treatment for

schizophrenia in India, despite the challenges associated with its use.

In another cross-sectional, non-controlled, non-interventional, hospital-based study which was conducted over a period of 18 months from November 2017 to May 2019 among the patients on clozapine. All the patients on clozapine, in the age group of 18 to 60 years, were interviewed. Total sample of 101 patients was evaluated and it was revealed that patients seem to tolerate and respond to higher doses of clozapineand the prevalence of blood dyscrasias in the study sample was much higher than the rest of India. [13]

In another cross-sectional retrospective study, aged 15–64 y, between October 2011 – October 2016, Only subjects with a diagnosis of schizophrenia who were prescribed clozapine were included in this analysis (n= 120). Clozapine was found to be more likely used in treatment resistant caseswith a chronic course of illness. Pattern of usage of clozapine remained the same in tertiary care setting. [14]

In an open trial, drug-resistant schizophrenics were treated with clozapine for sixteen weeks. The patients were rated on BPRS. Side effects scale and Global Impression Scale at weeks 0, 9 and 16. Of the total 29 included. 25 completed the trial.The patients showed significant improvement, although the improvement was more in initial weeks than between 9 and 16 week.[15]

Another study was done using a specifically prepared semi-structured performa containing 32 items and the questionnaire circulated to about 500 psychiatrists in India.A total of 117 responses were received in this study.

The study concluded that practice and usage of clozapine varies in Indian culture and the variation has no negative therapeutic effects.[16]

The study used a purposive sampling strategy which makes it vulnerable to selection bias, nonresponse bias, and voluntary bias. These could have been controlled if the study had used a random sampling strategy. Also given the number of practicing psychiatrists in India the sample seems to be low which affects the generalisability of the results. A merit of the study is that it had representation from almost all of India.

The study concludes that although numerous studies have proven clozapine to be an effective drug in management of psychosis its usage in Indian context remains subject to varying perceptions of different psychiatrists. Side effects and need to perform repeated investigations add to the barrier to its usage.

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