International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Usage of Clozapine in Clinical Practice – A Cross-sectional Study in a Tertiary Care Centre in India

Kusuma Malan[1], Zoyanakhat Mujahid[2], Sagar Karia[3], Sushma Sonavane[4]

[1] Class 1 Psychiatrist, Regional Mental Hospital, Thane.
[2] Assistant Professor, Department of Psychiatry, Farookh Academy of Medical Education, Hospital and Research Institute, Mysuru.
[3] Assistant Professor, Department of Psychiatry, LTMMC & GH, Sion, Mumbai.
[4] Additional Professor, Department of Psychiatry, LTMMC & GH, Sion, Mumbai

OPEN ACCESS

Corresponding Author:

Dr. Sagar Karia
Assistant Professor, Department of Psychiatry, LTMMC & GH, Sion, Mumbai.

Received: 14-10-2025
Accepted: 29-10-2025
Available online: 12-11-2025

ABSTRACT

Background: Clozapine is very useful antipsychotic in treatment resistant schizophrenia but its use is limited due to fear by psychiatrists of the life threatening side effects like agranulocytosis and myocarditis. Hereby we conducted this study to know the prescription pattern, doses, safety and efficacy of this drug. **Materials and Methods**: This was a cross-sectional study wherein patients who were on clozapine for at least a week were interviewed. Demographic details and details regarding clozapine (indication for use, starting dose, maximum dose, maintenance dose, side effects) were collected. Data was analysed using appropriate statistical tests. **Results**: 150 patients were enrolled in our study. Maximum had diagnosis of schizophrenia and related disorders (73.3%). Minimum dose used was 12.5 mg and maximum dose of 400mg was used in our study. Main indication to start clozapine was treatment resistance (53.7%). Main side effect reported was sedation (28.7%) followed by sialorrhea (20.7%). **Conclusions**: Clozapine is a well-tolerated drug with good efficacy and can be used as add-on with other drugs safely.

Keywords: *Clozapine, tolerability, efficacy, side effects, dosing.*

INTRODUCTION

Second generation antipsychotics were introduced in clinical practice in early 1900s. Clozapine being the prototype of this group was discovered surreptitiously by Wander group of laboratories while screening the tricyclics for antidepressant activity but was differentiated from the rest due to its neuroleptic activity. [1,2]

Clozapine use in its initial days showed promising results to the clinicians with fewer relapses, lesser need for hospitalization & restraints and a better quality of life in those patients who were previously on other medications. A phenomenon called awakening was noticed where in patients with chronic schizophrenia who were resistant to treatment showed symptom remission, complete functional recovery and resumed work. This gave hope for a better prognosis in chronic indolent schizophrenia.[1,2]

Much to the clinicians' disappointment clozapine also was associated with some serious and fatal side effects like agranulocytosis and myocarditis and some disabling side effects like excessive sedation and sialorrhea. Deaths being reported due to Agranulocytosis led to the withdrawal of the drug.[2]

All these gave rise to the pressing need for newer drugs which led to the discovery of other atypical antipsychotic drugs like Risperidone, Quetiapine, Olanzapine, Aripiprazole & Ziprasidone.[1]

Clinicians were so dreaded by Clozapine in the initial years, stringent measures and strict monitoring had to be done before dispensing the drug. Clozapine got its FDA approval in the year 1990 soon became popular in several countries.

Inspite of several studies like CATIE showing that clozapine is probably the most effective drug and so many other studies advocating the safety of clozapine, its use is limited to only a relatively small proportion of patients. [1,2]

Perhaps this molecule is looked up as a double edged sword; our study was an attempt to know the prescription pattern, doses, safety and efficacy of this drug. In the light of dearth of literature about this drug in recent years, the current study could be useful to know more about the drug & its usage in a tertiary care centre like ours.

MATERIALS & METHOD

This study was carried out in psychiatry outpatient department of a tertiary health care institute after obtaining Institutional Ethics Committee approval. This was a cross sectional study carried out for a year and patients who were on clozapine for at least a week and had a reliable informant with them were included in the study. The survey questionnaire was used to collect data after obtaining written informed consent from the participants.

Demographic details and phenomenological details like diagnosis, duration, co-morbidities, substance use, and questions related to clozapine use like reason for starting clozapine, starting dose, maintenance and maximum doses and side effects if any were collected.

Clinical Global Impression Scale-Improvement (CGI-I) was used to assess the clinical efficacy of clozapine as perceived by the relatives after starting the drug.

The data obtained was entered in excel sheet and analysed using computerised software. Frequency and percentages were calculated for categorical variables and mean and standard deviation were calculated for continuous variables. Comparisons were done using Chi-square test & t-test and p value of <0.05 was considered as statistically significant.

RESULTS

150 patients were included in our study. Table 1 describes the demographic details of study population. Our study comprised of patients mostly belonging to the age group of 24 to 48 years and coming from lower socio economic strata and males being more in number. Majority of patients (70%) who were on clozapine suffered from schizophrenia & related disorders followed by Bipolar mood disorder (13%) [Table 2]. Patients with MR with behavioral issues had been on clozapine for the longest followed by schizophrenia and related disorders. Diabetes was the most common co-morbid medical condition followed by hypertension. More than half (53.7%) of the study population had to be started on clozapine in view of treatment resistance, next most common indication being extra pyramidal side effects. Around 10% of patients were started on clozapine as they were actively suicidal [Table 3]. Table 4 describes the dose of clozapine received by study population. Majority of the patients (90.6%) had a mean starting dose of about 25mg of clozapine and majority (30%) were maintained at 100mg. Maximum dose of clozapine used in our study was 400mg. More than 85% of the study population had perceived improvement of grade 1 and 2 and above on CGI improvement scale [Table 5]. Most common side effect observed was sedation followed by sialorrhea [Table 6].

TABLES:

Table 1: Demographic details of our study population:

Parameter (N = 150)		**Mean ± S.D./ Frequency (%)**
Age (in Years)		34.64 ± 12.61 (14 - 68)
Education (in Years)		9.12 ± 5.36 (0 - 43)
Gender	**Male**	115 (76.7%)
	Female	35 (23.3%)
Marital Status	**Married**	85 (56.7%)
	Unmarried	65 (43.3%)
Religion	**Hindu**	120 (80%)
	Non-Hindu	30 (20%)
	Primary Schooling	7 (6.3%)

Table 2: Duration of illness & clozapine use in various disorders:

Parameter	**Schizophrenia & related disorders**	**Bipolar mood disorder**	**Major depressive disorder**	**MR with behavioral issues**	**P value**
Duration of illness (in years)	12.33 ± 9.75	10.33 ± 11.88	6.93 ± 5.28	9.83 ± 5.67	0.202
Duration of clozapine use (in years)	3.59 ± 4.38	1.76 ± 1.92	1.14 ± 1.12	7.34 ± 7.10	0.005*

Table 3: Reason for starting clozapine:

Indication (N=150)	Frequency	Percent
Treatment resistance	86	53.7
EPR	27	18
Suicidal thoughts	14	9.3
Aggression	8	5.3
Tardive dyskinesia	7	4.7
Negative symptom	4	2.7
Parkinson's disease	3	2.0
Insomnia	1	0.7

Table 4: Dose of clozapine in study population:

N=150	Mean ± SD	Range
Starting Dose	26.16mg ± 12.06	12.5 –150mg
Maintenance Dose	112.83mg ± 69.377	25 – 350mg
Maximum Dose	119.83mg ± 72.543	25 – 400mg

Table 5: Efficacy of clozapine in study population:

CGI Improvement	Diagnosis			
	Schizophrenia & related disorders	Bipolar mood disorder	Major depressive disorder	MR with behavioral issues
1	69	13	10	0
2	31	4	4	4
3	4	2	1	1
4	6	0	0	1
Total	110	19	15	6

Table 6: Side effects observed with clozapine in study population:

Side effects	Number of patients (%)
Sedation	43 (28.7)
Sialorrhea	31 (20.7)
Giddiness	13 (8.7)
Weight gain	1 (0.7)
Confusion	1 (0.7)

DISCUSSION

Clozapine is effective in treating both positive and negative features; has an upper hand over other atypical antipsychotics because of its almost nil propensity to cause EPR and ability to treat Tardive dyskinesia. A study done by Fitton A & Heel RC corroborates these properties of clozapine.[2] It is one of the most essential nevertheless most feared atypical antipsychotic in clinical practice. In a study done by Mortimer A et al. only over a half of patients with treatment resistance received clozapine.[3]

Nevertheless it is also associated with unfavorable side effects such as excessive sedation, giddiness, seizures, weight gain and insulin resistance which are also risk factors for Type II Diabetes mellitus and cardiovascular diseases. In a similar naturalistic study done by Henderson DC et al., 36.6% of the patients developed Diabetes mellitus over a 5 year follow up. [4]

In our study, majority of the population belonged to the age group from 24 to 48 years. Similar studies done by Mackin P et al., & Ciaparelli A et al., also consisted of people in similar age group.[5,6]

In our study before they were started on clozapine, most of the patients had been on a combination of 2 or 3 neuroleptics as well as some adjuvant drugs. Then they were shifted to or augmented with clozapine. Similar to a study done by Howes et al., in which Before commencing clozapine, antipsychotic polypharmacy and high-dose treatment was evident in 36.2 and 34.2% of patients respectively.[7] Majority of patients on clozapine had schizophrenia and related disorders. The most common reason for initiating clozapine being treatment resistance. Also patients with schizophrenia had to be started on clozapine much later than other illnesses probably because clozapine is considered not as the first line in the treatment. In a survey done by Kane JM, Leucht S, Carpenter D, Docherty JP which involved sending out questionnaires to expert panels, 88% of them endorsed risperidone and other atypical antipsychotics as the first line of schizophrenia and clozapine and other long acting atypical antipsychotics as the second choice.[8] On the contrary a study done by Wang PS et al., which was a cost benefit analysis of clozapine and other atypical antipsychotics suggests that it is beneficial if

clozapine is used as a first line drug since it would lead to much lesser loss of lives owing to its anti suicidal property, reduced relapses and no propensity to cause EPR.[9] However patients with bipolar mood disorders in our study had to be started earlier & almost half of patients were started on clozapine for reasons other than treatment resistance like EPR(25%), tardive dyskinesia(10%) & others. This is in accordance with this study done by Casey et al., which states that patients with affective disorders are more prone to get EPR & TD.[10]

Given that TD is one of the most distressing and disabling side effects of antipsychotics, it is said to be cured by clozapine. 7 patients had been on clozapine exclusively for Tardive dyskinesia. In a study done by Spivak B et al., at the end of 18 weeks of clozapine treatment, 74% of patients with Tardive dyskinesia and 69% of those with Parkinsonism showed improvement on AIMS scale & Simpson angus rating scale for EPS which was statistically significant.[11]

In our study most patients (83.33%) with MR with behavioral disturbances have been started on clozapine in view of EPR. A study done by Scheifes A et al., Almost half (44.0%) of 134 in-patient adults with ID and behavioral problems had any movement disorder.[12] Also they have been on clozapine for long time without any adverse effects. Similar results were produced by a study done by Midbari et al., Yalcin O et al., which says that the hematological abnormalities in the children were mostly transient, and that treatment with clozapine can be safely continued or renewed and since it has the least potential to cause EPR & tardive dyskinesia it is the better choice in children considering the fact that their duration of treatment is longer than that of adults.[13,14]

Suicidality was the major reason for starting clozapine in patients with Major depressive disorder in our study. Approximately 50% of patients with Schizophrenia and Schizoaffective disorder attempt suicide. Meltzer HY et al did a multicenter, randomized, 2-year study which compared the suicidal risks in Clozapine treated patients v/s Olanzapine treated patients. In this study suicidal behaviour was significantly less in patients treated with clozapine v/s olanzapine, fewer clozapine treated patients attempted suicide, required hospitalisations or rescue interventions to prevent suicide or required concomitant treatment with anxiolytics or snit depressants.[15] This supports the use of clozapine for suicidal thoughts in our study.

Treatment resistance was the indication for clozapine in 1 patient in this group who had OCD with severe aggression and self harming behavior who did not respond to optimum trial of both typical and other atypical antipsychotics. Contrary to the common belief that clozapine is known to unmask or aggravate OC symptoms, a study done by Ghaemi SN et al., shows that in 142 randomly selected in-patients who were started on clozapine treatment there were no definitive cases of patients who developed obsessive compulsive disorder (OCD) or whose OCD worsened as a result of clozapine treatment.[16]

Majority of them were started with 25mg/day and 1 patient was started on 150mg/day in view of aggression along with 2 other antipsychotics. In a retrospective analysis of 331 schizophrenics by volavca after an average of 47 wks of treatment, aggression rate had fallen down from 31.4% to less than 1.1%.[17] However a study done by Istyan Bitter et al., which was a prospective observational study shows that risperidone and olanzapine were superior to clozapine. And it also mentions that the relative non response to clozapine might have been limited to the study population alone.[18]

The starting, maintenance & maximum dose were higher in males. In a study done by Malalagama G et al., which investigated the prescription patterns of clozapine in males and females, it was found that majority of the sample population were males(69%) also they required a higher dose of clozapine. The mean dose per age group was higher in males in any age group.[19]

Patients with bipolar mood disorder required more than those with schizophrenia. Patients with MR with behavioral issues had received much lesser doses than the rest probably because of the already lowered seizure threshold in them. In a retrospective study done by Randall D. Buzan et al., only 1 patient with MR out of 10 developed seizures on 225mg of clozapine and he remained seizure free on clozapine after starting valproate.[20]

In our study more than 50% of the patients perceived improvement of Grade IV & above on Clinical Global Impression (improvement) scale. A study done by John Kane et al., which was a double blind randomized control study with 268 patients with treatment resistance, 33% of patients had remission compared to only 4% of patients of chlorpromazine.[21]

McEvov et al. found that the patients who were on drugs like olanzapine, risperidone & ziprasidone discontinued the use because of inadequate efficacy. The time before discontinuation of clozapine was much longer than others 10.5m for clozapine, 3.3 months for olanzapine.[22]

Sedation and sialorrhea were the most common side effects of clozapine treated patients in our study. They were symptomatically managed and none of the patients had to stop the drug because of this. Although clozapine is dreaded for its side effects like agranulocytosis and myocarditis, none were reported in our study.

CONCLUSIONS

Our study shows that clozapine is one of the most effective antipsychotic and very well tolerated one. It can be used safely in patients with medical comorbidities and life threatening side effects which are dreaded by majority psychiatrists are rarely encountered in clinical practice.

The limitations of our study being cross sectional nature and single centered study. More and more centres should conduct similar studies to generate more evidence on the subject.

Funding: No funding received
Conflicts of Interest: No conflict of interest

REFERENCES

1. Marder S.R., Hurford I.M. & Van Kammen D.P (2009) Second generation antipsychotics. In B.J. Sadock & V. A. Sadock Baltimore (Ed), *Comprehensive Textbook of Psychiatry*. (9th edition, Volume II, pg. 3206 –3240). Lippincott Williams & Wilkins.
2. Fitton, A., & Heel, R. C. (1990). Clozapine. A review of its pharmacological properties, and therapeutic use in schizophrenia. *Drugs*, *40*(5), 722–747.
3. Mortimer, A., Singh, P., Shepherd, C., & Puthiryackal, J. (2010). Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. *Clinical schizophrenia & related psychoses*, *4*(1), 49-55.
4. Henderson, D. C., Cagliero, E., Gray, C., Nasrallah, R. A., Hayden, D. L., Schoenfeld, D. A., & Goff, D. C. (2000). Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *American Journal of Psychiatry*, *157*(6), 975-981.
5. Mackin, P., Watkinson, H. M., & Young, A. H. (2005). Prevalence of obesity, glucose homeostasis disorders and metabolic syndrome in psychiatric patients taking typical or atypical antipsychotic drugs: a cross-sectional study. *Diabetologia*, *48*(2), 215-221.
6. Ciapparelli, A., Dell'Osso, L., Pini, S., Chiavacci, M. C., Fenzi, M., & Cassano, G. B. (2000). Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. *Journal of Clinical Psychiatry*, *61*(5), 329-334.
7. Howes, O. D., Vergunst, F., Gee, S., McGuire, P., Kapur, S., & Taylor, D. (2012). Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *The British Journal of Psychiatry*, *201*(6), 481-485.
8. Kane, J. M., Leucht, S., Carpenter, D., & Docherty, J. P. (2003). The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. *The Journal of clinical psychiatry*, *64*, 5-19.
9. Wang, P. S., Ganz, D. A., Bonner, J. S., Glynn, R. J., & Avorn, J. (2004). Should clozapine continue to be restricted to third-line status for schizophrenia? A decision-analytic model. *Journal of Mental Health Policy and Economics*, 77-86.
10. Casey, D. E. (1988). Affective disorders and tardive dyskinesia. *L'encephale*, *14*, 221-226.
11. Spivak, B., Mester, R., Abesgaus, J., Wittenberg, N., Adlersberg, S., Gonen, N., & Weizman, A. (1997). Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism, and chronic akathisia in schizophrenic patients. *Journal of Clinical Psychiatry*, *58*(7), 318-322.
12. Midbari, Y., Ebert, T., Kosov, I., Kotler, M., Weizman, A., & Ram, A. (2013). Hematological and cardiometabolic safety of clozapine in the treatment of very early onset schizophrenia: a retrospective chart review. *Journal of Child and Adolescent Psychopharmacology*, *23*(8), 516-521.
13. Scheifes, A., Walraven, S., Stolker, J. J., Nijman, H. L., Tenback, D. E., Egberts, T. C., & Heerdink, E. R. (2016). Movement disorders in adults with intellectual disability and behavioral problems associated with use of antipsychotics. *Journal of Clinical Psychopharmacology*, *36*(4), 308-313.
14. Yalcin, O., Kaymak, G., Erdogan, A., Tanidir, C., Karacetin, G., Kilicoglu, A. G., ... & Uneri, O. S. (2016). A retrospective investigation of clozapine treatment in autistic and nonautistic children and adolescents in an inpatient clinic in Turkey. *Journal of Child and Adolescent Psychopharmacology*, *26*(9), 815-821.
15. Meltzer, H. Y., Alphs, L., Green, A. I., Altamura, A. C., Anand, R., Bertoldi, A., ... & InterSePT Study Group. (2003). Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial (InterSePT). *Archives of general psychiatry*, *60*(1), 82-91.
16. Ghaemi, S. N., Zarate Jr, C. A., Popli, A. P., Pillay, S. S., & Cole, J. O. (1995). Is there a relationship between clozapine and obsessive-compulsive disorder?: a retrospective chart review. *Comprehensive psychiatry*, *36*(4), 267-270.
17. Volavka, J. (1999). The effects of clozapine on aggression and substance abuse in schizophrenic patients. *Journal of Clinical Psychiatry*, *60*(12), 43-46.
18. Bitter, I., Czobor, P., Dossenbach, M., & Volavka, J. (2005). Effectiveness of clozapine, olanzapine, quetiapine, risperidone, and haloperidol monotherapy in reducing hostile and aggressive behavior in outpatients treated for schizophrenia: a prospective naturalistic study (IC-SOHO). *European Psychiatry*, *20*(5-6), 403-408.

19. Malalagama, G., Bastiampillai, T., & Dhillon, R. (2011). Clozapine prescription patterns in Australia over the last 10 years. *Australian and New Zealand Journal of Psychiatry*, *45*(6), 498-499.
20. Buzan, R. D., Dubovsky, S. L., Firestone, D., & Dal Pozzo, E. (1998). Use of clozapine in 10 mentally retarded adults. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(1), 93-95.
21. Kane, J., Honigfeld, G., Singer, J., & Meltzer, H. (1988). Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Archives of general psychiatry*, *45*(9), 789-796.
22. McEvoy, J. P., Lieberman, J. A., Stroup, T. S., Davis, S. M., Meltzer, H. Y., Rosenheck, R. A., ... & Catie Investigators. (2006). Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *American Journal of Psychiatry*, *163*(4), 600-610.