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Clozapine Utilization Pattern in A Tertiary Hospital in North Central Nigeria: A 10 Year Retrospective Study

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ABSTRACT

Clozapine therapy remains a vital transformative, life-saving advancement in the treatment of resistant schizophrenia and other psychotic disorders among mentally ill-patients. This retrospective descriptive study was aimed at determining the frequency of utilization of clozapine among the study participants and to describe their socio-demographic and clinical correlates. We reported 32 participants who were in-patients at various times during a 10-year study period of January 2012 to December 2021 and were treated with clozapine at the Federal Medical Centre, Makurdi. The study had case files of participants retrieved after a manual search of all patients treated with clozapine from the in-patient register. Relevant socio-demographic and clinical data were obtained and analysed using SPSS version 23.We found a rate of 1,300/100, 000 (1.3%) use of clozapine, out of which 20(62.5%) were males while 12(37.5%) were females. Majority (81%) of the participants were aged 22-39years.There was a statistically significance difference between the mean duration of hospitalization before and after clozapine therapy respectively (p=0.04). Half (50%) of the participants had a diagnosis of schizophrenia while the rest had variable diagnoses like Bipolar disorder, Schizoaffective disorder and Substance related disorders. Eighty-four percent of the participants were stable and were discharged on clozapine therapy. Availability, accessibility and increased, timely prescription of clozapine by psychiatrists when indicated will shorten duration of hospitalisation as well as improve patient's outcome.

Keywords: Clozapine; Hospital; Pattern; Nigeria; Tertiary; Utilization.

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INTRODUCTION

The burden and unmet needs of patients with schizophrenia and related disorders continue to pose evolving challenges in psychiatric practice.[1]However, the discovery of antipsychotic medications generally in the 1950s revolutionized the treatment of psychiatric disorders particularly psychotic disorders leading to the closure of madhouses in Europe and America.[2, 3, 4]These first generation antipsychotic medications, though revolutionary, left much to be desired as some patients with schizophrenia and related disorders were not responsive to adequate doses of these conventional antipsychotics even in combination therapy and for adequate duration and observed strict medication compliance. This led to the diagnostic rubric of resistant schizophrenia, in which schizophrenia fails to respond to adequate trials of 2 or more conventional antipsychotic medications for 4-6 weeks.[5, 6]Clozapine became a landmark revolutionary drug treatment for resistant schizophrenia after a long, chequered and unexciting history.[7]Clozapine therapy is important for the following reasons:

Clozapine is the gold standard treatment for resistant schizophrenia.[8]Treatment-resistant schizophrenia is common in psychiatric practice with a prevalence rate of 30%, though various prevalence rates have been described in the literature ranging between 10% and 60%.[9, 10.]50% of treatment-resistant psychosis and 76% of treatment-intolerant patients responded well to clozapine[10]

Secondly, it is indicated for the treatment of schizoaffective disorders.[8]Schizoaffective disorder is frequently misdiagnosed and it accounts for 10-30% of in-patients with psychosis.[11]schizoaffective disorders also present considerable challenge of management in psychiatric practice with a significant proportion receiving a misdiagnosis for another mental disorder[12]Clozapine is also indicated for the treatment of suicidality or aggressive behaviours in patients with schizophrenia.[13-15.]Up to 28% of the premature deaths in schizophrenia can be attributed to suicide[16] and a lifetime prevalence of suicide in schizophrenia has been put at 4.9%[17]while aggressive behaviours in a meta-analysis is put at 15.3%–53.2%[18]Clozapine was found to be significantly more efficacious and tolerable than other antipsychotic drugs. A systematic review and Meta-analysis showed that clozapine was more effective than conventional antipsychotics in reducing symptoms both in treatment-resistant and non-treatment-resistant patients[19,20.]

Clozapine use is not devoid of problems. Its use comes with additional inconveniences of weekly blood tests by the patients in the first eighteen weeks, and more than weekly blood tests subsequently. This implies additional inconveniences of collecting blood sample from the patient weekly, and increased transport cost to the hospital. The implication is increased cost of treatment and a likelihood of poor medication compliance in low-income countries like Nigeria. Clozapine administration also comes with its own unique side effect profile like sedation, sialorrhoea, metabolic syndrome, cardiovascular side effects, and a rare life-threatening agranulocytosis and other blood dyscrasias. Evidence exists, however, that patients consider these additional inconveniences and side effects of clozapine to be worth the trouble than being treated with other antipsychotics.[21,22.]

The discovery of clozapine, with its far-reaching, evidenced-based benefits in psychiatric practice is well documented, established and internationally accepted and it has reduced this burden significantly. Despite the applause for clozapine, much is yet to be seen and reported about its utilization globally, much less in Nigeria. Although clozapine utilization has increased in many countries, international data still shows that clozapine is generally underutilized with variable rates across cultures and countries and even a decreased in utilization rate in some countries[23, 24]. The highest rate was reported in Finland and the lowest rate in Japan[25]. It is unclear why the rate of use of clozapine is widely variable among countries. Various reasons have been reported. These include stringent prescribing regulations and guidelines in some countries; limited training of prescribers, poor experience and low confidence among prescribing clinicians, fear of fatal agranulocytosis and occasional non availability of clozapine among others.[26]

There is paucity of information on utilization of

clozapine in Nigeria. Only one study from Sokoto looked at clozapine utilization[27]hence, this study is aimed at determining the rate of use of clozapine in Federal Medical Centre, Makurdi in a 10-year retrospective period and also to describethe socio-demographic and clinical correlates of the study participants.

MATERIALS AND METHODS

This is a retrospective descriptive study involving 32 participants. The in-patient registers of all admissions from January 2012 to December 2021 in the Department of Psychiatry, Federal Medical Centre (FMC), Makurdi were retrieved and examined. All consecutive patients treated with clozapine during the period were identified with their hospital numbers and a total of 32 patients were arrived at. Their case notes were retrieved for extraction of socio-demographic (age, sex, ethnicity) and clinical data. Clinical data include diagnoses, duration of hospitalization before and after commencement of clozapine and eventual treatment outcome for the participants. All in-patients who received antipsychotic medications other than clozapine were identified and a total of 2,456 were arrived at. The data was entered into SPSS version 23 for analysis. Descriptive statistics like frequency, ranges, mean were generated. Comparison of means was done using t-test and significance level was set at $p< 0.05$. Relevant tables and charts were also generated. Ethical approval was obtained from the Health Research and Ethics Committee of the FMC, Makurdi. Ref No: FMH/FMC/HREC/VOL I. Date: 21st April, 2022.

RESULTS

A total of 32 participants were recruited during the study period. Majority of the participants were males 20 (62.5%), while 12 (37.5%) were females. Participants aged 22-39 years were in the majority 24 (75%) while those who were above 40 years were 8 (25%). Tivs were 18 (56.3%), Idomas were 11 (34.4%), while other ethnic groups constituted 3(3.1%) as shown in Table 1.

The duration of hospitalization ranges from 1 week to 22.1 weeks for all participants in the study. The mean duration of hospitalization before commencement of clozapine therapy was 7.76 ±4.21 weeks and 4.35±2.35 weeks after commencement of clozapine therapy.This difference was statistically significance (p=0.04) as shown in Table 2.

Out of the 32 participants, half 16 (50%) had a dianosis of schizophrenia; 6(18.8%) had chronic psychotic disorder; 5 (15.6%) had Bipolar Mood Disorder (BMD), 3(9.4%) had schizoaffective disorder; 1(3.1%) had organic psychotic disorder (HIV related) and 1(3.1%) had Substance Use Disorder (SUD) as shown in figure 1.

Of the 32 participants, majority 27(84.4%) recovered and were discharged; 3(9.4%) were discharged against medical advice (DAMA); 1(3.1%) was transferred to another hospital and, another 1(3.1%) discontinued his treatment due to financial difficulties as shown in figure 2. Clozapine utilization rate was 1,300/100,000

Table 1: Socio-demographic characteristics of participants

S/n	Variable	Frequency	Percentage (%)
1.	**Age (years)**		
	22 -29	12	37.5
	30 -39	12	37.5
	≥40	8	25.0
	Total	**32**	**100.0**
2.	**Sex**		
	Male	20	62.5
	Female	12	37.5
	Total	**32**	**100.0**
3.	**Ethnicity**		
	Tiv	18	56.3
	Idom a	11	34.4
	Igede	1	3.1
	Igala	1	3.1
	Hausa	1	3.1
	Total	**32**	**100.0**

Table 2: Distribution of participants by Duration of hospitalization before and after clozapine therapy

S/N	Weeks	Frequency	Percentage
1.	**Pre -clozapine**		
	2.29	1	3.1
	2.60	2	6.3
	3.00	1	3.1
	3.40	1	3.1
	3.90	1	3.1
	4.40	5	15.6
	5.10	1	3.1
	6.40	2	6.3
	6.60	1	3.1
	7.00	1	3.1
	7.10	1	3.1
	7.40	1	3.1
	8.90	6	18.8
	9.10	1	3.1
	9.90	1	3.1
	10.60	1	3.1
	12.00	1	3.1
	13.30	3	9.4
	22.10	1	3.1
	Total	**32**	**100.0**
2.	**Post -clozapine**		
	1	3	9.4
	1.90	1	3.1
	2.00	3	9.4
	2.10	3	9.4
	3.00	4	12.5
	3.40	2	6.3
	3.90	1	3.1
	4.40	8	25.0
	4.70	1	3.1
	5.00	1	3.1
	6.00	1	3.1
	8.6	1	3.1
	8.90	1	3.1
	13.30	1	3.1
	22.10	1	3.1
	Total	**32**	**100.0**

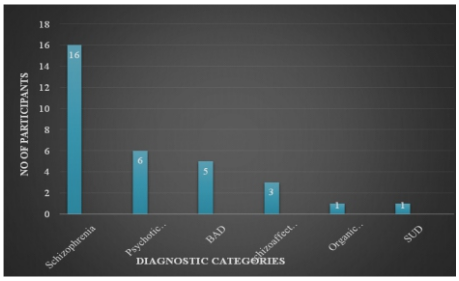

Fig. 1: *Various diagnoses of participants*

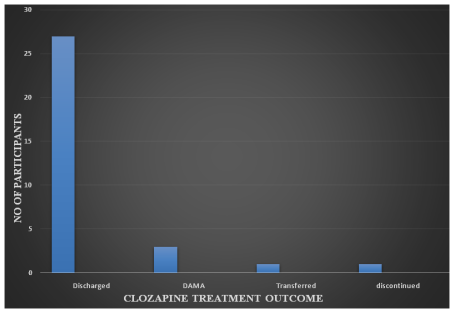

Fig. 2: *Clozapine treatment outcome of participants*

DISCUSSION

Bachmann et al. (2017)[25] method used in this study for the rate of utilization of clozapine found a rate of 1,300/100,000 population. This method was used based on a global prevalence of schizophrenia of 0.5-0.7%. It is difficult to compare our rate with a raw figure of 70 patients reported I n Sokoto by Yerima and colleagues in a decade experience of the use of clozapine in a tertiary hospital.[27]To the best of the authors' knowledge, there is no other study in Nigeria that looked at Clozapine utilization rate by which we can compare data. Over the years, globally, there appears to be an increasing utilization pattern of clozapine among the countries studied, the medication is generally underutilized. International data[25]from 17 countries puts Clozapine utilization rate in Finland at 189.2/100,000 and in New Zealand it was 116.3/100,000. In US, it was 40/100,000 and the lowest was in Japan at a rate of 0.6/100,000. In UK 65/100,000, Germany 95/100,000 and Australia 40/100,000. It is difficult to report with certainty the reason for the higher clozapine utilization rate in our study compared to data from US, UK and other parts of Europe, seeing that the utilization rates vary widely among these countries. The difference in our study with data from high-income countries could possibly be due to less stringent prescribing regulations in Nigeria compared to the high-income countries. Global trend shows increasing clozapine utilization, in most countries studied. The increased usage of clozapine is between 7.8-197.2% from 2005 t0 2014.[25]Again, prescribing guidelines and regulations seem to be more stringent in western countries than in Nigeria, where thereis no law specifically guiding prescription of specific drugs.[28]

Male participants were found to be more than female participants in this study. This observed preponderance of males over females in is similar to findings from studies on psychiatric patients from many tertiary departments of psychiatry in Nigeria[29-31]however, studies from Illorin and Ibadan showed the opposite[32, 33]. The commonest age is 22-39 years, constituting 78.1% of the participants. The participants in our study were younger than clozapine users from high-income countries, reported to be highest among 40–59-year-olds.[25] This

difference could be due to the pattern of psychiatric admissions in Nigeria where majority of hospitalised patients with psychiatric disorders are younger than 45 years[31, 32]and possibly a general reflection of the lower life expectancy in Nigeria[34] compared to high-income countries. The participants are predominantly Tivs and Idomas (56.3% and 34.4% respectively). These constitute the major ethnic groups in the study area and Benue State.

The mean duration of hospitalization pre-clozapine therapy was 7.8 weeks. After commencement of clozapine therapy, the mean duration reduced to 4.4 weeks. This difference was found to be statistically significant (p=0.04). This means that participants were hospitalised for longer periods, until clozapine therapy was commenced. This is in keeping with evidence from many other studies[35-37]

Half (50%) of the participants had a diagnosis of schizophrenia and had failed to respond to at least 2 conventional antipsychotics for more than 6 weeks before commencement of clozapine. This finding is in agreement with the main indication and licensed use of clozapine[38]

CONCLUSION

Despite the superior benefits of clozapine, global utilization is still low and our study shows a higher clozapine utilization rate in Makurdi compared to that of many studies elsewhere. Under-prescription of clozapine for mentally ill patients has implications for poor patient outcome, longer duration of hospitalization, re-admission and increased burden on the care givers. Although more research on clozapine is needed, there is need for prescribers to give patients increased access to clozapine. This implies more deliberate clozapine programmes in tertiary hospitals in Nigeria.

RECOMMENDATIONS

More researches are recommended on clozapine utilization among prescribing physicians. Psychiatrists and physicians who prescribe clozapine need to possibly increase patients' access to clozapine without delay.

Limitations

The study would have been more robust if the number of admissions per participant before and after commencement of clozapine were explored, but that information was not available retrospectively.

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Conflict of interests

The authors declare no conflict of interest.

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