Outcomes of Clozapine Treatment in Ethiopia: A Retrospective Study

A Thesis Submitted to the Department of Psychiatry, School of Medicine, College of Health Sciences, Addis Ababa University, in Partial Fulfillment of the Requirements for the Specialty Program in Psychiatry

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COLLEGE OF HEALTH SCIENCES

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Acronyms

AAU	Addis Ababa University
AMSH	Amanuel Mental Specialized Hospital
ACh	Acetylcholine
CHS	College of Health Sciences
APDs	Antipsychotic Drugs
CZP	Clozapine
DR	Dopamine Receptor
EKGH	Ekka-Koteb General Hospital
EDHS	Ethiopian Demographic and Health Survey
EPSE	Extra-pyramidal side effect
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric Acid
DNA	Deoxyribonucleic Acid
JUMC	Jimma University Medical Center
LAI	Long-acting injections
MRN	Medical Record Number
NMS	Neuroleptic Malignant Syndrome
PI	Principal Investigator
SCMHC	Sitota Center for Mental Health Care
SOM	School of Medicine
SPSS	Statistical Package for the Social Sciences
PD	Parkinson Disease
TRBD	Treatment-Resistant Bipolar Disorder
TRS	Treatment-Resistant Schizophrenia
ZMH	Zewditu Memorial Hospital

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Abstract

Background:- Clozapine is a second-generation antipsychotic drug which was introduced in 1961. It has wide clinical utility particularly for patients with treatment-resistant schizophrenia. Prescription of clozapine shows a considerable variation across countries. There is a general delay in its initiation partly because of its adverse effects, unavailability of clozapine and psychiatrist attitudes towards the medication. Many studies have investigated clinical characteristics, adverse effect profile and treatment outcomes over time internationally. However, to the best of our knowledge, there is only one institution based study in Ethiopian.

Objective: To assess the outcomes of clozapine treatment in five health facilities in Ethiopia.

Method: A retrospective chart review was conducted from May to October, 2020 on patients who have been treated with clozapine between 2017 to 2020. Data extraction sheet was used to extract secondary data to assess indications, adverse effects and treatment outcomes of patients treated with clozapine . SPSS version 25 was used for data entry and analysis.

Results: A total of 84 patients treated with clozapine were recruited and the main indications were treatment resistant schizophrenia(TRS) n=60 (71%), treatment resistant schizophrenia with tardive dyskinesia (TD) n=13(15.5%) and tardive dyskinesia n=10(11.9%). Seventy two (85.7%) patients had improvement of admission complaints upon discharge. The main improved symptoms were positive psychotic symptoms n=67(79.8%), negative symptoms n=52(61.9%), aggression n=33(39.3%), suicidal behavior n= 11(13.1%), depressive symptoms n=20(23.8%) and improvement of cognitive function n= 22(26. 2%). In case of TD patients, a mean AIMS score of 17.3 at admission reduced to 5.5 upon discharge. The most common side effects were sedation n=46(54.8%),sialorrhea n=31(36.9),constipation n=24(28.6%),weight gain n=18(21.4%) and transient hematological abnormalities n=14(16.7%). Serious side effect found were seizure n= 4(4.8%), persistent tachycardia n= 2(2.3%) and myocarditis n= 1(1.2%)

Conclusion and Recommendation:

Clozapine was indicated for treatment of TRS and TD, which resulted in improvement of admission complaints. Most of the side effects were tolerable and manageable. The main identified reason for discontinuation of the medication was unavailability. Having seen the indications, tolerable adverse effects and better treatment outcomes of clozapine, we recommend that patients with TRS and TD to be enrolled in clozapine treatment as soon as treatment-resistance is confirmed.

1.Introduction

1.1. Background

Clozapine is a dibenzodiazepine second-generation antipsychotic that was introduced in 1961 and approved by Food and Drug Administration (FDA) for its antipsychotic use in 1990. This antipsychotic is characterized by multi-receptorial with great affinity for dopamine-1 and dopamine-4 receptors than dopamine-2,unlike other second-generation antipsychotic drugs (1). It also has an affinity for a number of other receptors, such as serotonergic receptors, adrenergic receptors, muscarinic receptors and histaminergic receptors. This typical and atypical nature makes the drug more effective than any other antipsychotic in the management of treatment-resistant schizophrenia and other psychiatric disorders(1,3).

The primary clinical utility of clozapine is for patients with treatment-resistant schizophrenia (TRS) and schizoaffective disorder, who had persistent moderate-to-severe delusion and hallucination (2). This drug also alleviates negative symptoms as well as reduce risk of suicide, general psychopathology, low propensity to induce extra pyramidal symptoms (EPS) and hence reduces mortality compared to other antipsychotic drugs (APDs) (3).

Studies show that clozapine is also an effective agent for bipolar disorder , depression with psychosis , personality disorders, Parkinson's disease with psychosis and it has been used to decrease the number of violent episodes in patients regardless of their psychiatric diagnosis and even without psychotic symptoms(4).

Additionally, a systematic review conducted in China among 1044 treatment-resistant bipolar disorder patients reveals that clozapine was effective in improving symptoms of mania, depression, rapid cycling and psychotic symptoms, achieving a remission and improving quality of life (5).

Clozapine has cognitive restorative effect for patient with schizophrenia that present with cognitive dysfunction. This restorative effect of clozapine could be explained by interactions with the cholinergic system by increasing ACh release though indirect mechanisms of different neurotransmitters and long-term effects of gene expression (6).

Despite clozapine being used for treatment of a wide range of treatment resistant psychiatric disorders ,it is not being taken as a first line treatment due to its adverse effects. The adverse effects range from bothersome side effects like sedation, weight gain and sialorrhea to a potentially dangerous and life-threatening side effects like agranulocytosis or granulocytopenia,myocarditis, seizures, gastrointestinal hypomotility and others(7).

In addition to the difficulties related with adverse effects , clozapine requires regular blood monitoring and some patients with TRS might not respond for the medication(8).

Starting clozapine treatment at a younger age , providing longer treatment, developing new test tools that predict responders to clozapine and early detection of patients who are more prone to develop side effects may be associated with better clinical outcomes(9).

Clozapine treatment service has started in Ethiopia in 2017 and the service is also initiated at Amanuel Mental Specialized Hospital for the first time and then in selected governmental hospitals like Zewditu Memorial Hospital,Eka-Kotebe General Hospital , Jimma University Medical Center and Sitota Center for Mental Health Care ,which is the only private mental health facility that deliver clozapine treatment service .

To use clozapine safely, the Ethiopian Psychiatric Association (EPA) developed a guideline in October 2016 in recognition of the need to support and provide a regulatory framework for clinicians working in public and private settings. The guideline states that clozapine is indicated for treatment resistance or intolerance in schizophrenia and schizoaffective disorders, chronic risk of suicide and Parkinson's disease associated with psychosis.(10)

1.2. Statement of the Problem

Even though clozapine is the gold standard treatment option in patients with TRS and other non-clozapine resistant psychiatric disorders, it has dramatically divergent prescription patterns across countries and a general delay in its initiation. The possible reasons reported were that some psychiatrists may have different attitudes towards the advantages and disadvantages of clozapine while others may have less knowledge and experience to detect adverse effects of clozapine and its management(11).

Related with the above reasons and other unidentified factors, psychiatrists reported that they would use clozapine after three and more antipsychotics have failed(12, 13).The other important reasons for underuse of clozapine are client-related factors, of which medication discontinuation due to adverse effects and the need for regular blood test for monitoring the drug side effects are common reasons. This poor treatment adherence in patients with TRS and other psychiatric disorders may increase the risk of relapse, hospitalization, treatment costs as well as impaired social and cognitive functioning (7). To improve the prescription pattern and minimize possible associated adverse effects of clozapine, studying the existing treatment outcomes and related aspects is of paramount importance.

1.3. Significance of the Study

Despite clozapine being the most effective and gold standard second-generation antipsychotic drug for treatment-resistant schizophrenia in particular and other psychiatric problems such as schizoaffective disorder, Parkinsonism with psychosis, bipolar disorder and tardive dyskinesia,and reducing suicide, it is associated with potentially life-threatening adverse effects deserving special attention. This makes clozapine an underprescribed or underutilized antipsychotic agent(12, 13).

Many worldwide studies have investigated clinical characteristics, side effects and patterns of its use. However, to the best of our knowledge, no nation-wide study has been conducted in Ethiopia on treatment outcomes of clozapine. The aim of this study is to assess the indication, adverse effects and treatment outcomes among patients treated with clozapine in Ethiopia. The results show indications and outcomes of clozapine treatment. It is also expected to increase mental health professionals' awareness about the drug in the Ethiopian context and motivate them to optimize and practice safe prescription of clozapine. Additionally, it may serve as a gateway for other studies related to clozapine. The study will also provide baseline data to shade light on the utilization of the national clozapine guideline at varied institutions with the hope of giving direction to policymakers and regulatory bodies to improve the current clozapine treatment service.

Research Question

What are the treatment outcomes of clozapine treatment in Ethiopia?

2. Literature Review

There are number of studies done on clinical characteristics, adverse effects and treatment outcomes of clozapine(CZP) treated patients in different countries. Nevertheless, there is only one retrospective chart review done in our country Ethiopia on initiating clozapine treatment service and characteristics of clozapine-treated patients.(33).

A study conducted in Denmark from six counties involving 372 psychiatrists to assess their attitude towards and experiences with clozapine showed that 100 of them would use clozapine. They also reported that 99 (99%) would use it for TRS, 19 (19%) for schizoaffective disorder, 17 (17%)for bipolar disorder, 4 (4%) for tardive dyskinesia (TD) and 3 (3%) for suicidality (11).

In a retrospective study done at Christ church Hospital, New Zeal on 353 patients to evaluate the indication, dose and use of drug concentration monitoring of clozapine, it was shown that psychiatrists ordered it for treatment-resistant bipolar disorder (TRBD), treatment-resistant schizoaffective disorder and psychosis of Parkinson's disease (PD).The mean daily dose was 325 mg per day(SD-177 mg, range 12.5-900 mg)(14).

Another retrospective study conducted at University of Kansas Medical Center and Colorado Neurological Institute on 172 advanced PD patients treated with CZP and who had different psychiatric and neurologic problems showed that modest improvement in neurologic problems, psychotic symptoms improvement in 89.5% of patients with visual hallucinations, in 88.9% with auditory hallucinations and in 90.6% with delusions . It also showed improvement among 13.9% of patients with Akathisia and 60.4% in patients with depression (15).

In a case series study at Toronto Western Hospital, Canada on 8 PD patients with resting tremor, non-respondent to anti-Parkinson medications, it was shown that following initiation of clozapine, 3 patients had their tremor abolished while the tremor score decreased by an average of 64% in the remaining 5 patients, even if the mechanism remains unclear (16).

A retrospective chart review study conducted on 22 patients treated with clozapine at Zewiditu memorial hospital in Ethiopia, revealed that the main indications were TRS (15/22, 68.2%) and TD (7/22, 31.8%). In this study, patients showed improvement of admission complaints upon discharge which was measured by significant reduction of clinical global impression scale for incase of TRS and reduction of AIMS average score from 16.8 at admission to 6.5 at discharge incase of patients with TD(33).

A systematic review conducted in China on 1044 TRBD patients who had received clozapine treatment revealed improvement in symptoms of depression, mania , psychotic symptoms, reduction in aggressive behavior, suicidal ideation, reduced number and duration of hospitalizations and resulted in improvement in social functioning. In the same study different adverse effects were detected like leukopenia (2%), agranulocytosis (0.3%), seizure (0.5%) , no case of myocarditis and non-life threatening adverse effects, such as sedation (12%), constipation (5%), sialorrhea (5%), weight gain (4%), pain (2%), dizziness (0.5-1%) and diarrhea (1%) were also exhibited(5).

A retrospective study at Zewditu Memorial Hospital, Ethiopia on a total of 22 patients with a diagnosis of TD and TRS showed that development of non life threatening and serious adverse effects. The main non-life threatening side effects were Sedation 8 (36.36%) followed by constipation 6(27.27%) and excessive salivation 2 (9.09%), on the other hand, serious side effects developed were persistent tachycardia with EEG abnormality 1 (4.54%) ,cough, fever and tachycardia 1 (4.54 %) and persistent tachycardia with inadequate improvement 1(4.54%) (33).

A cross-sectional study done in New Zealand on 37 patients of which some of the patients were taking clozapine with doses ranging from 100 to 750 mg for at least three consecutive months, while others were on non-clozapine antipsychotics for a similar duration. After three months, all non-clozapine treated patients had normal colonic transit time while the majority of patients treated with clozapine (80%) was> 65 hours (2 SD above the population mean)(17).

In addition, a meta-analysis on the prevalence and risk factors of clozapine-associated constipation showed that the collective prevalence of constipation was 31.2%, which is higher than the general population (14.7%–17.1%) and three fold that associated with other antipsychotics. In this meta-regression analysis, hospitalization settings were found to correlate with the prevalence of constipation: inpatient (40.5%, 95%), outpatient (26.2%, 95%) and in mixed settings (22.2%). Age, sex, diagnosis, smoking, treatment duration and dose did not predict constipation rate (18).

A systematic review of 37 articles consisted of case reports and studies evaluating autonomic dysfunction and other cardiovascular side effects correlated with clozapine treatment revealed that 16(of 37) studies have reported cardiovascular related side effects found clozapine (CLZ)-induced tachycardia, arrhythmia, myocarditis and orthostatic hypotension (19).

Another study conducted at Uppsala, Sweden, to assess the prevalence of tachycardia in patients treated with clozapine and long-acting inject able (LAI) antipsychotics for the management of

schizophrenia showed that 33% of patients who took clozapine and 16% of those on LAI antipsychotics developed tachycardia (HR>100)(20).

Another study which was done in Iceland, on 201 patients with schizophrenia treated with clozapine and 410 patients with schizophrenia treated with other antipsychotics but who had never been on clozapine. After an average follow up time of 9.2 years,34 patients developed neutropenia, of which 24 developed mild neutropenia (1500–1900 neutrophils/mm3) and 10 patients developed neutropenia in the range of 500–1400/mm3. Only one patient developed agranulocytosis from the 10 patients who developed neutropenia(500–1400 /mm3),three stopped clozapine use and the remaining 6 patients continued clozapine without developing agranulocytosis.Both groups had an equal risk of developing neutropenia (21).

A retrospective study at a tertiary care hospital in North India which was done to assess the prevalence and incidence of seizure in 222 patients for whom clozapine was prescribed, showed that most were male (65%), single (65%) and unemployed (57%); new-onset seizure with clozapine was seen in 6% of the patients, most of which were male. The study also revealed that the prevalence of seizure had significant association with the dose of clozapine: 3% with doses up to 300 mg/day, 8% with 325 to 500 mg/day and 38% in those receiving > 500 mg/day(22).

A systematic review of published literatures between 1972 and 2011 on 138 patients with schizophrenia spectrum disorder to analyze the outcome of clozapine rechallenge after they developed severe adverse effects. After the patients were followed for 16–96 weeks, clozapine rechallenge was successful in 69.6% patients after neutropenia (78 in 112), 20% after agranulocytosis (3 in 15), 100% after NMS (all 5) , 75% after myocarditis (3 in 4). None of the re-challenged patients died (23).

A large-scale epidemiological study conducted at South London and Maudsley NHS Foundation Trust (SLAM) electronic health records (EHR) done to verify the shielding effect of clozapine on mortality in 2837 TRS patients, of which 1025 were clozapine group and 1812 were non-clozapine group. These two groups were compared and the clozapine group had more regular face-to-face clinical contact, less severe psychopathology profiles, lower substance use disorders, better indices of living conditions and good social relationships than the non-clozapine group (24).

Based on a systematic review done in the State of Maryland involving 1287 Caucasian and 588 African American patients who started clozapine, 48.6% of African American and 44.9% of Caucasian patients discontinued clozapine at some point for any reason. On this review, clozapine

underutilization and discontinuation was associated with low efficacy, agranulocytosis, leucopenia, other hematologic and non-hematologic adverse effects(25).

A systematic review of 15 papers published from 1972 to2018 was done to study the barriers to clozapine use and interventions in treatment-resistant schizophrenia on 608 male and 402 female patients. The studies consist of different populations, settings, periods, and methodologies. The review showed that barriers are possibly related with clinician, patients and health system factors. From patient related factors, complete refusal of blood tests was considered a major barrier (56%) and complication-related barriers were found to be 37%. On the other hand, the common clinician-related factors were fear of side-effects and lack of knowledge in dealing with severe adverse effects (26).

3.Objectives

3.1.General Objective

To assess the outcomes of clozapine treatment in five health facilities in Ethiopia

3.2.Specific Objectives

- To assess indications for clozapine treatment
- To assess treatment response of patients treated with clozapine
- To evaluate the adverse effect profile of patients treated with clozapine

4.Methodology

4.1.Study Setting

The study was conducted at four governmental and one private hospital in Ethiopia where clozapine treatment service is provided. The hospitals that deliver clozapine treatment service in Addis Ababa are Amanuel Mental Specialized Hospital, Ekka-Kotebe General Hospital, Zewditu Memorial Hospital and Sitota Center for Mental Health Care. Jimma University Medical Center is the only institution that provides clozapine treatment out of Addis Ababa.

Amanuel Mental Specialized Hospital (AMSH)

Amanuel Mental Specialized Hospital is the first psychiatric hospital in Ethiopia. It was established by Italian invaders while the country was occupied by Italy from 1935-1940 for general purpose and it was transformed to a specialized psychiatric hospital in 1948. The hospital has a capacity of 261 beds with a total number of 953 employees, among which over 500 are clinical staffs including 12 psychiatrists, 1 neurologist,17 general practitioners, 32 MSc psychiatry professionals,7 health officers and 12 BSc psychiatry professionals. The hospital gives service in different case teams including outpatient, inpatient and 24-hour emergency psychiatry units. One of such case teams is the psychosis case team, which is led by a psychiatrist and is staffed by psychiatrists, residents, nurses and clinical psychologists. Clozapine treatment was initiated under a separate case team in 2017.

Ekka-Kotebe General Hospital (EKGH)

This hospital began operation in 2017. It is equipped with 350 beds, of which 175 are for psychiatry and the remaining beds are for other health services. The psychiatry department is staffed by 3 psychiatrists,1 neuropsychiatrist, varying numbers of psychiatry residents and consultant psychiatrists, 11MSc psychiatry professionals, 10 BSc psychiatry professionals nurses, 4 clinical psychologists, 5 general psychologists and 4 social workers. The psychiatry department has different case teams to give outpatient, inpatient and 24-hour emergency services. The hospital has started clozapine treatment service since mid-2018.Currently this hospital is serving as COVID -19 treatment center and the mental health service shifted to Global which is owned by Ekka-Kotebe General Hospital as eye tratment center previously .

Zewditu Memorial Hospital (ZMH)

Zewditu Memorial Hospital (ZMH) is located in Kirkos Subcity at the center of Addis Ababa, Ethiopia. It was built, owned and operated by the Seventh-day Adventist Church. It was inaugurated on January 26, 1971 as Empress Zewditu Memorial Adventist Hospital, nationalized during the Derg regime in 1976, and is now one of the five hospitals under the Addis Ababa Health Bureau.. It provides different health services and serves as a training cite for residents of Addis Ababa University (AAU) in different specialties, including mental health. The psychiatry service is organized into adult and child outpatient clinics as well as inpatient services of detoxification and clozapine. The clozapine inpatient service has started in 2016. The mental health services are delivered by 1 addiction psychiatrist,2 consultant psychiatrists,1 clinical psychologist, psychiatry residents and clinical psychology students from AAU together with 6 BSc psychiatric nurses and a clinical psychology professional from ZMH.

Jimma University Medical Center (JUMC)

This hospital is located in the southwest part of Ethiopia, which is 357 km away from the capital city of Ethiopia. It is the only teaching and referral hospital and referral center for the southwestern part of the country. It provides services for approximately 9000 inpatient and 80,000 outpatient attendees a year. The psychiatry department gives both outpatient and inpatient services for more than 30 million people. Clozapine treatment service in this hospital was started in 2019.

Sitota Center for Mental Health Care (SCMHC)

Sitota Center for Mental Health care is one of the largest private psychiatric centers in Ethiopia that provides different mental health services to the community. The center has 45 beds structured into 3 wards and is equipped with psychiatrists, clinical psychologists and psychiatry nurses. This private mental health hospital provides different services of which inpatient and outpatient service of alcohol and drug rehabilitation, adult and child psychiatry, psychotherapy, training and post-discharge support are among the main services that the center deliver for the urban and rural community. The center also provides clozapine treatment service for those who have access to the medication from abroad.

4.2.Study Period

The study was conducted from May to August,2020 on patients who have been treated with clozapine between 2017 to 2020, i.e. starting from the launching of clozapine services up until the time of data collection, August 2020 .

4.3. Study Design

A retrospective char review was conducted.

4.4.Study Population

The study participants were patients who have received clozapine treatment at AMSH, EKGH , ZMH ,JUMC and SCMHC.

4.5.Sample Size Determination

The sample size was considered to be all patients who have been treated with clozapine at the aforementioned healthcare facilities until the end of the study period.

4.6.Sampling Technique

All patients who have been treated with clozapine at AMSH, EKGH , ZMH ,JUMC and SCMHC were included from the start of clozapine treatment up to the time of data collection, August 2020. A total of 92 medical record numbers (MRN) of the patients treated with clozapine since the start of the medication to the time of data collection were identified from each hospitals' registration books and were given to record officers to collect the charts. The identification was done by the PI for the facilities found in Addis Ababa and by data collector for JUMC**.** A total of 8 charts were excluded, 4 charts due to incompleteness of data and the remaining 4 charts due to mismatch between recorded MRN on registration book and patient charts and missing of old charts. Finally, 84 charts were selected and reviewed for this study .

4.7.Inclusion and Exclusion Criteria

This study used secondary data extracted from patient medical records.

Inclusion Criteria

Patients who were treated with clozapine for any psychiatric diagnosis.

Exclusion Criteria

Patient charts with considerable incomplete or missed data which make it difficult to meet the research objective(s)/ answer the research question.

4.8.Data Collection

Secondary data of patients who have been treated with clozapine at the specified healthcare facilities were collected from charts using the data extraction sheet prepared for that purpose**.** The data was collected from patient medical records by the PI for all sites except Jimma, where data was collected by MSc psychiatry professional.

4.9.Data Collection Tool

Data extraction sheet was prepared depending on the objectives of the study containing mainly two sections, i.e. socio-demographic and clinical data. The questions comprise duration of the treatment, dose of the medication, clinical characteristics, documented adverse effects and outcome as well as other different parameters.

4.10.Data Management and Analysis

The PI did the data cleaning, entry and analysis using the Statistical Package for the Social Sciences (SPSS) version 25. Frequencies, percentages, means and ranges of different variables were computed for description.

4.11. Dissemination and Utilization of Results

The findings from this study will be presented to the Department of Psychiatry,AAU and AMSH. A copy of it will be sent to JUMC ,EKGH, ZMH and SCMHC. Due efforts will also be made to publish the study on a peer-reviewed journal**.**

5.Ethical Considerations

Ethical clearance was obtained from the Scientific Committee of the Department of Psychiatry, SoM, CHS, AAU and the ethics review boards of AMSH and JUMC. Permission was also asked from EKGH, ZMH and SCMHC to access patients' medical records. No personal identification of the study subjects was recorded and all the data collected from the medical records of the study participants will be kept confidential.

6. Results

Socio-demographic characteristics of participants

A total of 92 charts of patients treated with clozapine were identified from hospital registration and data collection and analysis was done on 84 charts. The patients were recruited from all health facilities that give clozapine treatment in Ethiopia, i.e. AMSH (n=41,48.8%), ZMH (n=18,21.4%),SCMHC (n=15,17.9%) , JUMC(n=6,7.1%) and EKGH(n=4,4.8%).

A majority of the participants (n=70,83.3 %) were male and (n=14,16.7%) were female. The age of the participants ranged from 20 to 55 years, with a mean age of 35.12 years ±8.13SD. among the participants (n=38 ,45.2 %) were in the age group of 30-39 years and (n= 5,6.0 %) were above 50 years of age.

Most (n=59,70.2%) of the participants were residents of Addis Ababa and (n=17,20.2%) were from different regions receiving clozapine treatment in Addis Ababa, while (n=7,8.3%) of them were from Jimma.

Nearly half (n=47,56.0%) of the participants were Orthodox Christians, followed by Muslims(n=21, 25.0%). Sixty-six (78.6%) of the participants were single while(n=10,11.9%) were married. Interns of educational background (n=22,26.2%) of the participants completed primary school(n= 26,31.0%) completed secondary school and (n=26,31.0%) of the respondents attended college and above. With regards to occupation(n= 54,64.3%) were unemployed and only (n=15,17.9%) were employed. The remaining details are displayed in Table 1.

Table 4: Socio-demographic data on patients treated with clozapine in Ethiopia, 2020.

Variables	Characteristics	Number	%
Sex	Male	70	83.3
	Female	14	16.7
Age group	Below 29	22	26.2
	30-39	38	45.2
	40-49	19	22.6
	50 and 0lder	5	6.0
Marital status	Single	66	78.6
	Married	10	11.9
	Divorced	8	9.5
Residence	Addis Ababa	59	70.2
	Jimma	7	8.3
	Other	17	20.2
	Unrecorded	1	1.2
Religion	Orthodox Christian	47	56.0
	Muslim	21	25.0
	Protestant	8	9.5
	Catholic	1	1.2
	Unrecorded	7	8.3
Educational status	No formal education	6	7.1
	Primary	22	26.2
	Secondary	26	31.0
	College and above	26	31.0
	Unrecorded	4	4.8
Employment status	Employed	15	17.9
	Unemployed	54	64.3
	Unspecified	11	13.1
	Unrecorded	4	4.8

Clinical Characteristics and Indication

The indications for clozapine treatment were TRS (n=60, 71.0%), TRS and TD (n=13, 15.5%) and TD (n=10, 11.9%) while the remaining (n=1, 1.2%) was treatment-resistant schizoaffective disorder. The total duration of illness before clozapine ranged from 1 to 31 years with a mean duration of 10.97 ± 6.89 SD. All participants (n= 84, 100.0%) were given a starting dose of 12.5 mg as per the protocol and the maximum dose ranged from 125 to 700mg with a mean of 397.92mg ±123.34mg SD. About the total duration of maximum dose the shortest was 1week,the longest was 6 years , below 3 months (n=33, 39.3%) and above 2 years(n=9,10.7%).

A majority of the patients (n=71, 84.5%) who have been on clozapine treatment were taking the medication for less than 1 year whereas (n=3,3.6%) have been taking it for more than 3 years.

Twenty-eight (33.3%) of the participants were still taking clozapine at the time of data collection while the remaining (n=56,66.7%) were no longer taking it. The main reason identified for the participants to discontinue the medication was unavailability of the medication (n=43, 76.8%) while other reason was reported to be side effects(n=4, 7.1%).

During the treatment course of clozapine(n= 40,47.6%) of the patients took other medications such as antidepressants (sertraline and fluoxetine) (n=16, 19.0%), anticonvulsants (Na Valpoarate) (n=6, 7.1%) and antihypertensive medications (hydrochlorothiazide and nifedipine) (n=6, 7.1%).

Among the patients(n=29,34.5%) had comorbid psychiatric disorders, including depressive disorders (n=14, 16.7%), substance use disorders (tobacco, cannabis, k hat) (n=14, 16.7%) and OCD (n=1, 1.2%). Twelve (14.3%) were reported to have comorbid chronic medical illness while 5(6.0%) had family history of psychiatric disorders.

Most (n=61, 71.6%) of the patients were treated bypsychiatrists while (n=19,22.6%) were treated by psychiatry residents under supervision of psychiatrists and(n= 4,4.8%) by clinicians with an MSc in psychiatry.

Table 5 Clinical characteristics of patient treated with clozapine in Ethiopia, 2020.

Variables	Characteristics	Number	%
Indication for clozapine treatment	TD	10	11.9
	TRS	60	71.4
	TRS and TD	13	15.5
	Others	1	1.2
Total duration of illness before clozapine	<5 years	24	28.6
	6-10 years	21	25.0
	11-15 years	19	22.6
	16-20 years	13	15.5
	>20 years	6	7.1
	Unrecorded	1	1.2
Clozapine starting dose (in mg)	12.5	84	100
Clozapine maximum dosein mg	<300	30	35.7
	301-400	20	23.8
	401-500	20	23.8
	501-600	13	15.5
	> 600	1	1.2
Total duration of maximum dose of clozapine	< 3 months	33	39.3
	3-6 months	14	16.7
	6months -1 year	24	28.6
	1-2 years	4	4.8
	> 2 years	9	10.7
Total duration of clozapine treatment	< 1year	71	84.5
	1 -2years	4	4.8
	2- 3years	6	7.1
	> 3years	3	3.6
Clozapine prescribed by	MScin Psychiatry	4	4.8
	Psychiatry resident	19	22.6
	Psychiatrist	61	72.6
Other medication with clozapine	Yes	40	47.6
	No	44	52.4
Patients currently on clozapine	Yes	28	33.3
	No	56	66.7
	Side effect	4	7.1
	Unavailability	43	76.8

Reason of discontinuation of clozapine treatment	Other	9	16.1
Co-morbid chronic medical illness	Yes	12	14.3
	No	72	85.7
Co-morbid psychiatric disorder	Yes	29	34.5
	No	55	65.5
Family history of psychiatric disorder	Yes	5	6.0
	No	46	54.8
	Unrecorded	33	39.3

Treatment outcomes of clozapine

A majority(n=72, 85.7%) of clozapine treated patients had improvement of admission complaints upon discharge whereas the remaining (n=11, 13.1%) had no documented change. The improved symptoms include positive psychotic symptoms (n=67, 79.8%), negative symptoms (n=2, 61.9%), cognitive function (n=22, 26.2%), homicidal/aggression (n=33, 39.3%), suicidal behavior (n=11, 13.1%) and depressive symptoms (n=20, 23.8%) of which (n=12,60%) were on anti-depressant and clozapine . In case of tardive dyskinesia,the mean AIMS scores at admission and upon discharge were17.3 and 5.5 respectively (Table 3).

Among the total participants(n= 69.82.1%) developed side effects and the commonest were sedation (n=46, 54.8%), followed by sialorrhea (n=31,36.9%),constipation (n=24, 28.6%),weight gain (n=18, 21.4%) and transient hematological abnormalities(n=14,16.7%) such as granulocytosis (n=9,10.7%),eosinophilia (n=3, 3.6%) and low platelet count (n=2, 2.4%).

On the other hand, 7 participants developed serious side effects such as seizure (n=4, 4.8%), persistent tachycardia (n=2, 2.3%) and myocarditis (n=1, 1.2%), which resulted in discontinuation of the treatment among (n=4, 4.8%) patients and none of them were rechallenged.

The common side effects were managed by dose adjustment (lowering, dividing, shift to night dose ,slow titration) (n=19, 27.3%),psycho-education, reassurance and repeated complete blood counts(n=18, 26.1%, while (n=9,13.0%) required pharmacologic interventions like prescribing bisacodyl and Na-valproate .

Table 6:Treatment outcome and side effects of clozapine among patients treated with clozapine in Ethiopia,2020.

Variables	Characteristics	Number	%
Treatment outcome upon discharge	Improved	72	85.7
	No change	11	13.1
	Worsen	1	1.2
Symptoms improved upon discharge	Positive psychotic symptoms	67	79.8
	Negative symptoms	52	61.9
	Cognitive function improvement	22	26.2
	Homicidal/Aggression	33	39.3
	Suicidal behavior	11	13.1
	Depressive symptoms	20	23.8
Current patient condition	On remission	34	40.5
	Worsen	16	19.0
	No change	27	32.1
	Other	7	8.3
AIMS score(N-23)	AIMS score at admission (mean)	17.3	-
	AIMS score up on discharge(mean)	5.5	-
No. of hospitalization(n-69)	Before clozapine treatment(mean)	3.35	-
	After clozapine treatment(mean) has started	0.196	-
Side effect developed	Yes	69	82.1
	No	15	17.9
Common side effects detected	Sedation	46	54.8
	Sialorrhea	31	36.9
	Constipation	24	28.6
	Weight gain	18	21.4
	Granulocytosis	9	10.7
	Enuresis	8	9.5

Measures taken for side effects	Dose adjustment (lowering ,dividing, night ,slow titration)	19	27.25
	Discontinuation of clozapine	4	5.8
	PE(diet, exercise...)	18	26.1
	laxative (bisacodyl)	8	11.6
	Other	5	7.2

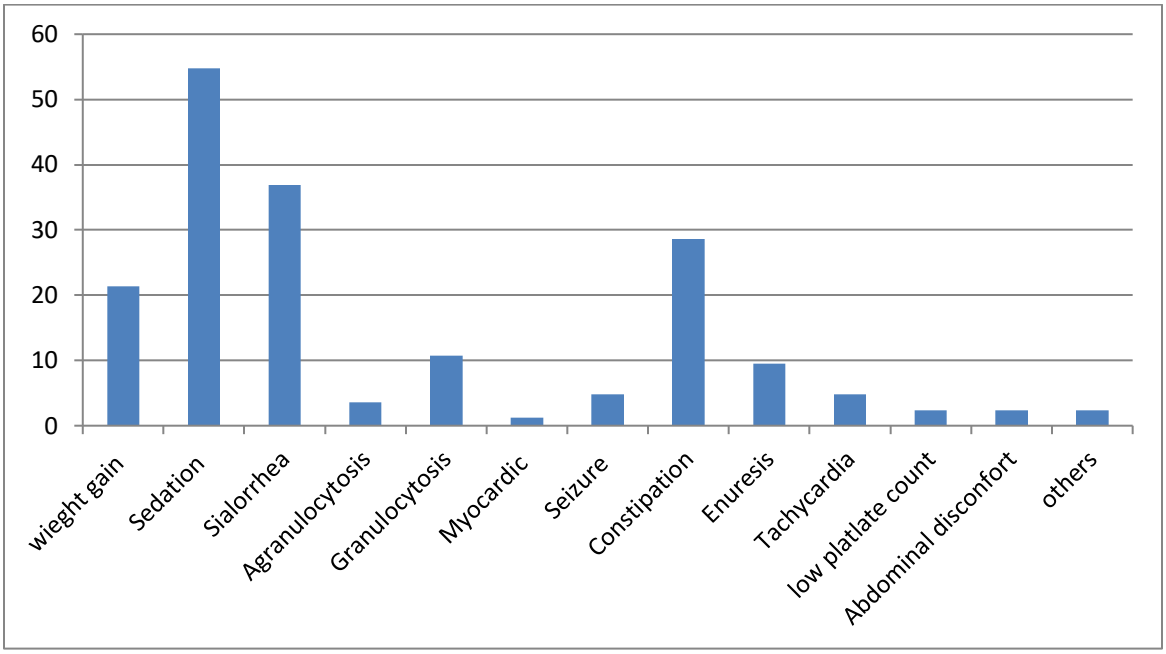

Figure 1: Side effects detected among patients treated with clozapine in Ethiopia,2020.

7.Discussion

The aim of this study was to assess clozapine treatment outcomes of patients at all health facilities providing the service in Ethiopia.

In this study the indications of clozapine treatment were TRS, TD , combination of TD and TRS and treatment-resistant schizoaffective disorder. Whereas studies showed that clozapine is used for a wide-range of psychiatric disorders such as TRS, schizoaffective disorder, bipolar disorder, depression with psychosis, personality disorders and Parkinson's disease with psychosis(11-17). Furthermore, it has been used to decrease suicidality and the number of violent episodes in patients regardless of their psychiatric diagnosis (4,11). Similarly other study done in New Zealand, psychiatrists use clozapine for treatment-resistant bipolar disorder (TRBD), treatment-resistant schizoaffective disorder and psychosis of Parkinson's disease (PD)(14).

Using clozapine for limited indications in our country Ethiopia could be justified by the treatment being used for the last four years in only 5 health facilities of which only one found out of the capital city of Ethiopia which creates difficulty to reach the majority of people who need the service. In existing few psychiatry hospitals, inpatient service is limited because of lack of beds, low number of psychiatrist, inconsistent availability of the medication and unwillingness of the caregiver to start clozapine since it requires repeated blood test and fear of side effect contribute a lot for this discrepancy.

In our study, majority of clozapine-treated patients had improvement of admission complaints upon discharge whereas the remaining less than 13% of patients had no documented change. The improved symptoms include positive psychotic symptoms, negative symptoms, depressive symptoms and cognitive function improvement. Besides, patients with homicidality /aggression and suicidal behavior were also found to have improvement. In line with this, a study conducted elsewhere on 84 patients with TRS, clozapine treatment has shown reduction in admission complaints (30). Other studies on clozapine also showed that it is effective for alleviation of both positive and negative symptoms, reduction of mortality by decreasing suicidality and aggression in patients with schizophrenia(3,31). Additionally, a study reviewed several case reports showed that improvement in negative and positive symptoms (32).

As our finding indicated, clozapine has cognitive restorative effect for patient with schizophrenia that present with cognitive dysfunction(6). Concerning patients with TD, AIMS score which was recorded on admission reduced significantly upon discharge in our study. A similar study on

clozapine in Ethiopia also revealed that patients who were diagnosed with TD, had significantly reduced average AIMS score at discharge (33). These findings further strengthen the existing evidence for clozapine for such indications.

The common side effects detected in this study were sedation 46(54.8%), sialorrhea 31(36.9),constipation 24(28.6%),weight gain 18(21.4%) and transient hematological abnormalities 14(16.7%) such as granulocytosis 9 (10.7%) ,eosinophilia 3(3.6%) and low platelet count 2(2.4%).

A hospital based retrospective chart review done in Ethiopia on a total of 22 patients with a diagnosis of TD and TRS showed that sedation 8 (36.36%), constipation 6(27.27%) and excessive salivation 2 (9.09%) were the detected common non- life threatening adverse effects(33).

These two studies found comparable result on constipation and significant different in the rest of non life threatening side effects. This could be due to difference in sample size even though the studies used similar study design and study population.

Likewise, a study conducted in china on 1044 TRBD patients the non-life threatening side effects found were sedation (12%), constipation (5%), sialorrhea (5%), weight gain (4%) and diarrhea (1%) (5). This relatively low percentage of side effects compared to our finding could be attributed to variation in genetics, diet, life style, hospital setting and wide range of sample size difference. Another evidence from a meta-analysis on the prevalence of clozapine-associated constipation revealed that the total prevalence of constipation was 31.2% (18). This finding is almost similar with the result of our study.

Serious side effects found in our study were seizure 4(4.8%), myocarditis 1(1.2%) and persistent tachycardia 2(2.3%) .

Similar to our finding , a retrospective study at a tertiary care hospital in North India done to assess the prevalence of seizure in 222 patients treated with clozapine, 13 (6%) of patients developed seizure (22).

On a study conducted in China, seizure (0.5%) was one of the gravest clozapine related side effects identified (5). This finding was slightly lower than the one reported in our study which could be explained difference in genetics, diet, life style, hospital setting and sample size.

Similar to our study finding, a systematic review of published literatures on 138 patients with schizophrenia spectrum disorder which showed that 4(2.89%) of the patients developed myocarditis (23).

In distinction to our study, a study done in Sweden to assess the prevalence of tachycardia in patients treated with clozapine illustrated that 33% of patients who took clozapine developed tachycardia (HR>100)(20). This difference could be attributed to the fact that our study documented those patients who had persistent tachycardia whereas the mentioned study assessed all patients who had any record of tachycardia during the course of clozapine treatment.

7.1 Strengths and Limitations of the Study

Strengths

Involving all governmental and private institutions that provide clozapine service in Ethiopia and collecting data from all patient charts starting from launching of clozapine service in Ethiopia are considered to be the greatest strength of this study.

Limitations

Since this is a retrospective chart review, the quality of documentation had a considerable impact on the quality of data obtained in this study. With the exception of AIMS scores for TD, it was difficult to administer tools to objectively measure other clinical outcomes.

8. Conclusion

The study found that the main indications for clozapine in Ethiopia were treatment-resistant schizophrenia (TRS),tardive dyskinesia (TD) and the combination of TD and TRS. Which shows that in our country Ethiopia, we used clozapine for limited psychiatry disorder treatment.

A majority of clozapine-treated patients had a documented improvement of their admission complaints upon discharge. Positive psychotic symptoms, negative symptoms, cognitive function, homicidal/aggression, suicidal behavior and depressive symptoms were the improved symptoms of patients with TRS.

In case of tardive dyskinesia clozapine indicated patients, the mean AIMS score at admission reduced significantly upon discharge. Two third of the total participants who have been on clozapine previously were not taking the medication at the time of data collection. The main identified reason for discontinuation of the medication was unavailability.

Most participants developed bearable side effects that could be managed by non-pharmacological measures. The commonest side effects detected were sedation followed by sialorrhea and constipation. On the other hand, only less than five percent of the patient developed life threatening side effects such as seizure and myocarditis.

9.Recommendations

Having seen the indications, tolerable and manageable adverse effects and better treatment outcomes of clozapine, we recommend for patients with TRS and TD to be enrolled in clozapine treatment as soon as it is noticed that they are not responding for other antipsychotic medications.

All stakeholders, including Ministry of Health, regional health bureaus, governmental and private hospitals, teaching institutions, Ethiopian Food and Drug Administration and the Ethiopian Psychiatric Association should have a collaborative effort to expand and improve the clozapine treatment service , securing availability of medication and ensure proper application of the national treatment guideline .

Psychiatrists

- Early identification and enrollment of patients who are treatment-resistant and who developed tardive dyskinesia into clozapine treatment service.
- Enhancing care givers' awareness on treatment options of treatment resistance and tardive dyskinesia

Hospitals and Higher teaching institutions

- Should work to establish inpatient psychiatry service including clozapine treatment
- Strengthen their laboratories with the necessary equipments and reagents to secure persistent lab services.
- Providing training for psychiatry nurses, clinical pharmacists and psychiatrists etc. who have no experience with the national clozapine treatment guideline.
- Advocating for and carrying out the necessary procedural measures for continued availability of clozapine in their pharmacies.
- Improve documentation of all relevant patient data for better evidence based planning and decision making.
- Hospitals should ensure clozapine treatment to be provided by physicians only as per the clozapine treatment guideline.
- Further research to generate better knowledge on associated factors and other related ideas.

Federal Ministry of Health

- Working to strengthen and expand psychiatry service including clozapine treatment in the country and securing availability the medication
- Encouraging researchers to conduct studies on clozapine

Annex:

Data extraction sheet

Questionnaire ID _____

Name of the Facility	_____
Medical Record Number	_____
Date of data collection	————/DD/————/MM/———/YY/

Part 1: Demographic and Socioeconomic Data

No.	Question and filters	Response/Choices	Skip
101	Age	_____years	
102	Sex	Male.....1 Female.....2	
103	Residence	Addis Ababa ……..……1 Region(specify)----------2 Jimma……...……3	
104	Religion	Orthodox…….1 Muslim……..…..2 Protestant……..…3 Catholic ……..4 Other (specify)_____5	
105	Educational status	Not formal education …….……..1 Primary……..2 Secondary……..……....3 Tertiary……..4	
106	Marital status	Single…….……1	

		Married …….....2 Divorced…….....3 Widowed…….....4	
107	Caregiver educational status	No formal education ……..…1 Primary……..2 Secondary……..……3 Tertiary……..4	
108	Occupational status (NB. more than one answer is possible)	House wife ……1 Farmer……2 Daily laborer.....3 Government/private employee…..4 Other specify…….……5 _____	
109	Occupational status of partner (NB. more than one answer is possible)	Farmer……...1 Daily laborer…….....2 Government/private employee…..4 Other (specify)……...5 _____	
110	Average monthly income	…….....Birr	

Part 2: Clinical Data		
No.	Question	Response
201	Type of diagnosis/side effect indicated for clozapine	_____
202	Date of diagnosis	_____/_____/_____
203	Total duration of illness before clozapine has been started	

		In years_____/ in months_____ or weeks_____
204	Currently on clozapine	Yes----------1 No----------2 Unknown------3
205	Date of start of clozapine	_____/_____/_____
206	Prescribed by	MSc Psychiatry Professional ----------1 Psychiatry Resident----------2 Psychiatrist----------3
207	Was the prescriber trained on clozapine?	Yes----------1 No----------2 Unknown----------3
208	Maximum dose of clozapine (mg)	_____
209	For how long on maximum dose	----------year(s) and month(s)----------week(s).....
210	Total duration of clozapine treatment	_____year(s)_____month(s)_____week(s) _____ other (specify)----------
211	Any adverse effect	Yes.....1 No.....2 If yes, please specify: Sedation----------1 Weight gain----------2 (Specify in kg--------) Sialorrhea----------3 Agranulocytosis----------4(Mention in --------cell/ mm3) Granulocytopenia----------5(Mention in --------cell/ mm3) Myocarditis----------6 Seizure----------7 Constipation----------8 Other (specify)----------9

212	When adverse effect detected (since initiation of clozapine)	----------week(s)
213	Any measure taken for the adverse effect (s)?	Yes----------1 No----------2
214	What measure was taken to manage the adverse effect(s)?	Lowering dose of clozapine----------1 Discontinuation of clozapine----------2 Other (specify)……3 _____ _____
215	Outcome of treatment (specify if, improved, worsened, etc)	Discontinued----------1 Improved ----------2 Worsened----------3 Other (specify) _____
216	If discontinued, reason of discontinuation:	Side effect(s)----------1 Unavailability----------2 Refusal of regular blood test ----------3 Other (specify)_____4
217	If refusal of blood test (reason of refusal)	Cost related ----------1 Shortage of lab reagent in hospital----------2 Other(specify)----------3
218	(If clozapine treatment was discontinued), time of discontinuation	_____week(s)
219	What improvement were seen (more than one answer is possible)	Hallucination----------1 Delusion----------2 Disorganized behavior ----------3 Negative symptoms----------4 Cognitive function ----------5 Homicidal /Aggression ----------6 Suicidal behavior ----------7, Other (specified)----------8

220	Was rechallenge tried after they developed side effect(s)?	Yes----------1 No----------2
221	If yes,what was the result?	Improvement of side effect----------1 Worsen ----------2
222	Other medications given(over the course of clozapine treatment)	Yes.....1 No.....2 If yes, please list 1.---------- 2.---------- 3.----------
223	Any comorbid chronic medical illness?	Yes.....1 No.....2 If yes, specify _____
224	Any comorbid psychiatric illness?	Yes.....1 No.....2 If yes, specify _____
225	Is the comorbid psychiatric disorder substance related?	Yes----------1, If yes, specify---------- No----------2
226	If yes (during clozapine treatment)	Yes----------1 No----------2
227	Family history of psychiatric illness	Yes.....1 If yes , specify---------- No.....2 Unknown……...3

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