Original Research Article

Perceived Awareness of Clozapine associated with Socio-Demographic status, clinical, and side effect profile among patients from Mental Health Hospital, Taif, Saudi Arabia

Javed Ather Siddiqui[1], Shazia Farheen Qureshi[2], Hani Matrok Alotaibi[3],

[1,2,3]Psychiatrist, Department Of Psychiatry, Mental Health Hospital, Taif, Kingdom Of Saudi Arabia
Corresponding author: Javed Ather Siddiqui
Email – Javedsiddiqui2000@Gmail.Com

ABSTRACT

Background: The main objective was to investigate the Socio-demographic, clinical, and side effect profile of patients on clozapine from Mental Health Hospital, Taif, Saudi Arabia. This article reports on an observational study. Clozapine is a second-generation atypical antipsychotic used as the drug of choice for the treatment resistant psychosis. It is supposed to be a baseline study from which we will get and understand rate of clinical, and side effect profile of the clozapine taking patients. Physicians, particularly psychiatrists are not only ignoring but also not aware, alert, so they always need to be watchful to the fatality of the drug, and take appropriate therapeutic measures. The aim was to study the socio-demographic status, clinical profile, comorbidity, side effects and outcome of patients treated with clozapine.
Methodology: We reviewed all the indoor psychiatric patients of Mental Health Hospital, Taif, Saudi Arabia, from the period of one year between January 2021 to January 2022 (N=29). Our study design focused on prospective and observational studies. Descriptive statistical analysis was explored, and presented as frequencies, and percentages. We also determined crude rates for all adverse outcomes of clozapine.
Results: We did a nearly mean follow-up of one year. The majority of patients were male (n=26; 89.65%), with a maximum being unmarried (n=16; 55.17%). Most patients belong to nuclear families due to cultural restrictions in this country (n=23; 79.31%). Among the literacy rate illiterate were (n=2; 6.89%, and unemployed (n=23; 79.31%). Among the study populations, the majority of respondents were found to have treatment-resistant schizophrenia (n=18; 62.06%), and around 79.31% of patients took more than two antipsychotics in adequate doses. Among side effect profiles most of the patients suffered hyper-salivation (n=19; 65.51%), sedation (n=12; 41.37%), and rarely suffered from agranulocytosis.
Conclusion: Socio-demographic, clinical, and side effect profiles were the significant indicators of clozapine. Clozapine has been used for treatment-resistant psychosis, but due to fatal side effect profile we used it cautiously. In our study, we found that myocarditis, hematemesis, and leukocytosis, and neutropenia are fatal side effects of clozapine. We also found hyponatremia-induced seizure. The prevalence of blood dyscrasias in our study is rarely seen. Hyper-salivation is the most common side effect reported. Majority of the patients in our study were male, and treatment resistant Schizophrenia was the most common diagnosis. Myocarditis is life-threatening side effect seen in our study.

Keywords: Clozapine, atypical antipsychotic, leukocytosis, myocarditis.

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INTRODUCTION

Clozapine (CLZ) is a tricyclic dibenzodiazepine, an antipsychotic drug. It is the first atypical, second generation antipsychotic prescribed for one to two thirds of patients with resistant psychotic Symptoms because of its therapeutic efficacy [1]. It works on many receptors including dopamine, serotonin, adrenergic, histaminergic and muscarinic receptors, and it is an odd agent among all antipsychotics [2, 3]. It is the drug of choice, and the gold standard medication for the treatment of resistant schizophrenia, as

well as the treatment of resistant bipolar disorder [4]. Among other indications are tardive dyskinesia [5], severe psychotic depression, idiopathic Parkinson's disease [6], Huntington's disease [7], pervasive developmental disorder, autism in childhood, and patients with extrapyramidal symptoms [8]. Additionally, clozapine has been shown to decrease the risk of suicide, excitement, aggressive behavior, and hostility in schizophrenia. It has also proven beneficial for treating schizophrenia patients with comorbid alcohol abuse and other drugs by reducing craving [9].

It has been at limited use because of the fatal side effect profile, some of which is potentially complicated and some of which needs monitoring after the medication has been started. Such side effects include sedation, fatigue, hyper-salivation, dizziness, hypotension, tachycardia, weight gain, nausea, vomiting, and constipation [10]. Another side effect is anticholinergic effects such as dry mouth, blurred vision, and urinary incontinence [11, 12]. Hematological side effects like agranulocytosis; blood dyscrasias including leukopenia, neutropenia, anemia, eosinophilia, and leukocytosis [13]. There are also metabolic abnormalities associated with clozapine-induced side effects like hypertriglyceridemia, hyperglycemia, and type 2 diabetes mellitus [14]. Gastrointestinal side effects such as constipation, esophagitis, ischemic colitis, paralytic ileus, gastroesophageal reflux disease, and hematemesis [15]. There are a number of genitourinary side effects, including priapism and incontinence [16]. Dermatological side effects include angioedema, acute generalized exanthematous reactions, Stevens–Johnson syndrome, and toxic epidermal necrolysis [17]. Cardiovascular side effects like tachycardia, hypotension, syncope, dilated cardiomyopathy, myocarditis, and pericarditis [18]. The possible reason for discontinuing clozapine is that some of the side effects are rare, fatal, miserable, and massive.

METHODOLOGY

Participants

Participants included in this study were male and female patients from inpatient's psychiatry wards from Mental Health Hospital, Taif, Saudi Arabia, and were assigned to take treatment between the periods from January 2021 to January 2022.

Parameters

We collected demographic data including age, gender, marital status, family type, occupation, education, and socioeconomic status. Clinical profile data like diagnosis, comorbidity, antipsychotics used prior to clozapine therapy, dosage range of clozapine in milligrams. We also collected data from the side effect profile of clozapine. The data were collected with face-to-face interviews on clozapine taking patients, physical examinations, and available laboratory investigations.

Inclusion Criteria

- Age range of participants was between 30 years to more than 65 years.
- Participants were from all communities of Mental Health Hospital, Taif, Saudi Arabia.
- Participants were included who were taking clozapine during the period 2021 to 2022.

Exclusion Criteria

- Age range of participants below the 20 years.
- Participants who are not taking clozapine.
- Patients who were acutely symptomatic and terminally ill like malignancy with advanced renal, hepatic, and cardiac diseases were excluded from the study.

Sampling Technique

Purposive sampling strategy adopted by researcher to select the participants from Mental Health Hospital, Taif, Saudi Arabia. Sample size was N=29, which included male, and female participants.

Research Instrument

The instruments which were used in this study were socio-demographic profile, clinical, and side effect profile forms. These forms filled up by researcher during taking face-to-face interview, and physical examination of clozapine taking patients.

Ethical Issues in Research

Current research was conducted with careful consideration. Participants were treated with respect. This research work started after the approval by the Ethical Committee of Research, and Studies Department, Directorate of Health Affairs, Taif, Saudi Arabia.

Procedure

All the patients on clozapine, in the age group of 30 to 60 years, were interviewed after taking written informed consent. The consent was taken in a local Arabic language which the patient understood, and they were given freedom of choice to accept or refuse participation in the study. There were a total of 29 patients who were on clozapine. All of the patients went through a detailed interview for socio-demographic characteristics followed by a general physical examination.

RESULTS

Socio demographic profile (Table 1)

Table 1: Socio-demographic profile of patients on clozapine

Demographic variables	Frequency (n)	Percentage (%)
Age in years		
30–39	14	48.27
40–49	8	27.58
50-59	5	17.24
>59	2	6.89
Gender		
Male	26	89.65
Female	3	10.34
Total	29	100.0
Marital status		
Married	8	27.58
Unmarried	16	55.17
Divorced	5	17.24
Total	29	100.0
Family type		
Nuclear	23	79.31
Joint	6	20.68
Total	29	100.0
Occupation		
Unemployed	23	79.31
Employed	6	20.68
Total	29	100,0
Education		
Illiterate	2	6.89
Primary	12	41.37
High school	11	37.93
Graduate	4	13.79
Total	29	100.0
Socioeconomic class		
Upper middle	12	41.37
Lower middle	17	58.62
Total	29	100.0

The demographic data are depicted in Table 1. The sample included 29 patients taking clozapine from Mental Health Hospital, Taif Saudi Arabia's inpatient psychiatric wards. In our study majority of patients were male respondents (n=26, 89.65%), and female patients participating were (n=3; 10.34%), and total

male, and female patients were 29 (N=29). The majority of (n=16; 55.17 %) respondents are unmarried; married are (n=8; 27.58 %), and divorced respondents are (n=5; 17.24 %). The maximum numbers of patient (n=14; 48.28%) are in 30-39 years' age group, and (n=8; 27.58 %) are 40-49 years' age group, and 17.24 percent are 50-50 years' age group, and 59 years above age group are 6.89 percent. Maximum number of the patients belonged to nuclear families (n=23; 79.31%), and joint family respondent were (n=6; 20.68%) Similarly, around three fourths of them were unemployed (n=23; 79.31%). Around (n=12; 41.37%) had passed primary school certificate, followed by high school educated are (n=11; 37.93%), and graduate respondents (n=4; 13.79%). Employed patients are (n=6; 20.68%), and (n=2; 6.89%) patients are illiterate. Most of the patients were smokers, and 50 percent of the patients attended to traditional faith healers before going to hospital.

Clinical profile (Tables 2, 3)

Table 2: The descriptive analysis according to diagnosis of patients on clozapine

Characteristic	TRS	TRBD	Schizophrenia with suicidality or aggression	Psychotic Depression
Age				
30-39 years	9	3	2	0
40-49 years	5	1	2	0
50-59 tears	3	0	1	1
>60 years	1	0	1	0
Gender				
Male	17	2	6	1
Female	1	2	0	0
Antipsychotics used prior to clozapine				
Haloperidol	10	2	4	0
Risperidone	11	4	2	1
Amisulpride	11	1	2	1
Quetiapine	8	1	3	1
Paliperidone	7	2	2	0
Aripiprazole	3	0	0	0
Chlorpromazine	2	0	2	0
Lithium	0	1	1	0
ECT	2	0	0	0

TRS: Treatment-resistant schizophrenia,
TRBD -Treatment-resistant bipolar disorder, **ECT:** Electroconvulsive Therapy

The clinical data are depicted in Table 2. In our study, most of the respondents are (n=18; 62.06%) are diagnosed treatment-resistant schizophrenia. (n=7; 24.13%) were diagnosed with schizophrenia with suicidality or aggression. (n=3; 10.34%) had treatment-resistant bipolar disorder, and (n=1; 3.44%) had diagnosed a psychotic depression. Maximum number of patients (n=21; 72.41%) had no medical comorbidity. All of our patients had received at least two antipsychotics before being started for clozapine therapy. But majority of patients were more than two antipsychotic used before starting clozapine, and two patients around 6.89 percent received electroconvulsive therapy and lithium before starting clozapine. The dosage of clozapine administered was between 50 to 600 mgs/day, the range between 101-200 mg were (n=6; 20.68%), between 201-300 mg were (n=8; 27.59%), between 301-400 mg were (n=9; 31.03%), between 401-500 mg were (n=5; 17.24%), and between 501-600 mg were (n=1; 3.44%). Higher doses of clozapine are used for the treatment-resistant schizophrenia and schizophrenia with suicidality or aggression.
This descriptive analysis can be summarized in table 3. The majority of patients seen in the 30-39 years' age group have treatment-resistant schizophrenia and treatment-resistant bipolar disorder. Psychotic depressive patient is seen in the 50-59 years' age group. Majority of male patients are seen in treatment-resistant schizophrenia, after that schizophrenia with suicidality or aggression, and majority of female patients are seen in treatment-resistant bipolar disorder. Maximum number of patients taking risperidone, and

amisulpride in treatment-resistant schizophrenia, and after that, haloperidol used prior to taking clozapine. Majority of patients have taken electroconvulsive therapy in treatment-resistant schizophrenia prior to taking clozapine. Lithium was used in treatment-resistant bipolar disorder and schizophrenia with suicidality or aggression.

Table 3: Clinical profile of clozapine taking patients

Clinical variables	Frequency (n)	Percentage (%)
Diagnosis		
Treatment-resistant schizophrenia	18	62.06
Treatment-resistant bipolar disorder	3	10.34
Schizophrenia with suicidality or aggression	7	24.13
Psychotic depression	1	3.44
Total	29	100.0
Comorbidity		
None	21	72.41
Hypothyroidism	3	10.34
Hypertension	3	10.34
Diabetes mellitus	3	10.34
Ischemic heart disease	1	3.44
COPD	1	3.44
Number of antipsychotics used prior to clozapine		
2 (two)	6	20.68
>2 (more than two	23	79.31
Total	29	100.0
Antipsychotic used prior to clozapine		
Risperidone	16	55.17
Haloperidol	15	51.72
Quetiapine	13	44.82
Amisulpride	11	37.93
Paliperidone	11	37.93
Aripiprazole	8	27.58
Chlorpromazine	4	12.79
Lithium	2	6.89
Electroconvulsive therapy	2	6.89
Dose range of clozapine (in mgs)		
<= 100 mgs	0	0
101–200 mgs	6	20.68
201–300 mgs	8	27.58
301–400 mgs	9	31.03
401–500 mgs	5	17.24
501–600 mgs	1	3.44

Table 4: Side effect profile of patients on clozapine

Side effect	Frequency (n)	Percentage (%)
Sedation	12	41.37
Hyper-salivation	19	65.51
Constipation	4	13.79
Hypotension	5	17.24
Weight gain	4	13.79
Tachycardia	5	17.24
Dry mouth	5	17.24
Dizziness	3	10.34
Leukocytosis	3	10.34

Nocturnal enuresis	1	3.44
Tremor	5	17.24
Neutropenia	1	3.44
Hyponatremia induced seizure	1	3.44
Akathisia	1	3.44
Myocarditis	1	3.44

Table 5: Analysis of risk factors in psychosis

Characteristic	Diagnosis	Number of patients/ 29	Leukocytosis	Neutropenia	Hyponatremia - induced seizure	Myocarditis	Hematemesis
Diagnosis	TRS	18	0	1	1	1	0
	TEBD	3	1	0	0	0	0
	Schizophrenia with suicidality or aggression	7	2	0	0	0	1
	Psychotic depression	1	0	0	0	0	0
Gender							
	Male	26	2	1	1	1	1
	Female	3	0	0	0	0	0
Dose							
	>400 mg	6	0	1	0	1	0
	<400 mg	23	1	0	1	0	1

The clinical data are depicted in Table 3. In our study, hyper-salivation, and sedation were most commonly seen side effect of clozapine (n=19; 65.51%), and (n=12; 41.37%) respectively, after that (n=5; 17.24%) developed hypotension, tachycardia, tremor, and dry mouth. A total of (n=4; 13.79%) patients developed weight gain while on clozapine. (n=3; 10.34%) developed dizziness, and leukocytosis, and (n=1; 3.44%) patient developed neutropenia, akathesia, and myocarditis. We also found that (n-1; 3.44%) patient developed hyponatremia-induced seizures. Patients took a mean 250 mg of clozapine per day developed leukocytosis. Patients taking the maximum dosage 500 mg had statistically significant neutropenia. Clozapine dosage is associated with different side effects. The side effects like sedation, hyper-salivation started with low dosage 25 mg of clozapine, and later subsided after increasing the dosage. Stuttering was not found in our study.

Analyzing risk factors are depicted in table 5. Neutropenia, myocarditis, and hyponatremia-induced seizures are seen in treatment-resistant schizophrenia. Neutropenia and, hyponatremia-induced seizures are seen with doses over 400 mg of clozapine, but not the other medications, patients taking less than 400 mg of clozapine developed leukocytosis and hematemesis. Male patients experience all fatal side effects such as neutropenia, myocarditis, hyponatremia-induced seizures, leukocytosis, and hematemesis.

DISCUSSION

In this study we examined the effectiveness, importance, and ever-increasing prescribing of clozapine in various psychiatric disorders. The majority of patients in this study were males, unmarried, and unemployed living in nuclear families, and belonging to lower socioeconomic groups. As stated earlier, treatment-resistant schizophrenia is the most common indication of clozapine use. The early onset of psychosis results in poor educational achievement, poor occupational, and social skills, which lead to not getting employment opportunities, and having difficulties in obtaining a job [19-20].

Maximum number of patients in our study had received more than two antipsychotics before starting on clozapine, which are second generation antipsychotics like risperidone. There is a maximum number of studies where patients had already tried many antipsychotics before starting clozapine [21, 22]. In our study we observed maximum number of atypical antipsychotics as well as closed number of typical antipsychotics also used before starting clozapine, and didn't find life-threatening conditions like Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) [23].

In our study risperidone was the first choice in our patients followed by haloperidol. Also in other studies there was risperidone as first choice of antipsychotics. Tardive dyskinesia (TD) is a hyperkinetic, involuntary, delayed onset, repetitive body movement disorder characterized by irregular, stereotyped, and choreiform movements due to use of antipsychotic medication. Now a day it is the common practice to stop the current antipsychotic, and to start clozapine for treatment of TD [24]. In addition to clozapine, there are a variety of medications that can alleviate the symptoms of TD, including highly selective monoamine transporter 2 inhibitors such as tetrabenazine and valbenazine; high doses of pyridoxine, and bilateral deep brain stimulation [25-28].

In our study we found common side effects of clozapine were hyper-salivation, sedation, constipation, nausea, nocturnal enuresis, seizure, hypertension, and tachycardia, and severe life-threatening side effects like myocarditis were found. There are different alternatives to treat treatment-resistant bipolar disorder; clozapine is one of the effective choices [29]. Other recommended treatment alternative is quetiapine [30], antimanic medications such as valproic acid, lithium, carbamazepine [31], and Electroconvulsive Therapy [32]. In our study, some patients were taking quetiapine, and antimanic medication along with clozapine therapy.

CONCLUSION

It is the responsibility of physicians, particularly psychiatrists, not only to be aware of this life-threatening side effect, and its consequences. But also to be alert, and watchful of the fatality of this drug, and take appropriate therapeutic measures as appropriate.so that the morbidity and mortality could be prevented. Therefore, raising awareness of clozapine's safety is crucial because it is the safest medication for treatment resistant psychosis if monitored appropriately.

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