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Profile of Clozapine Therapy: a Cross Sectional Piloting in a Tertiary Care Setting of Bangladesh

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1. Abstract

Clozapine is a very important atypical antipsychotic indicated for one to two third patients of resistant psychotic symptoms. It is also indicated in Treatment Resistant Bipolar Disorder (TRBD), Tardive Dyskinesia (TD) and few other indications. Most common side effects of clozapine are hypersalivation, sedation, constipation, hypertension, hypotension, fever, seizure, tachycardia, nocturnal enuresis and agranulocytosis. The study aimed to look into the patients getting clozapine in respect of demography, disease and side effects profile. This cross sectional study was conducted among 21 hospitalised patients those getting clozapine. The data were collected with semi structured questionnaire and preformed checklist through face to face interview, physical examination and available laboratory investigations. Majority of the patients were male and Resistant Schizophrenia was most common diagnosis. The

effective therapeutic dose was 50-200 mg/day in most cases (64%). Sedation (90.5%), hyper salivation (81%), constipation (81%), nausea (23.8%), nocturnal enuresis (23.8%), hypertension (9.5%), and tachycardia (28.6%) were the noted side effects. Among the developed side effects constipation and sedation occurred at lower dosage. Though the study sample is small, observed set of side effects are similar and coherent with existing evidences. Further broad based study needed to extract representative data that can be utilised in future clinical practice locally.

Keywords: Clozapine; Side effects; Bangladesh

2. Introduction

Bangladesh is one of the densely populated developing countries with about 160 million people [1]. The prevalence of mental disorder is 6.5 to 31.0% among adults and 13.4 to 22.9% among children in the country [1, 2]. As there is no national guideline, mental health care professionals follow the European or other guidelines during clinical practices. Though the debate regarding efficacy of FGA and SGA is still ongoing, clozapine is choice of drug in Treatment Resistant Schizophrenia (TRS). It is also effective in Treatment Resistant Bipolar Disorder (TRBD), Tardive Dyskinesia (TD) [3, 4]. Along with the common metabolic side effects [5], there are other specific side effects that hinder good compliance of the treatment. The common adverse effects of clozapine are sedation, hypersalivation, constipation, hypotension, hypertension, tachycardia, weight gain, fever, seizure, nocturnal enuresis, neutropenia/agranulocytosis, gastroesophageal reflux disease (GERD) [6-12]. The uncommon or unusual adverse effects are agranulocytosis/neutropenia, colitis, delirium, eosinophilia, heat stroke, hepatic failure, interstitial nephritis, ocular pigmentation, pancreatitis, parotid gland swelling, pericardial effusion, pneumonia, reflux esophagitis, stuttering, vasculitis and thrombocytopenia [6, 13-17]. Serious haematological and cardiovascular adverse effects are agranulocytosis, thromboembolism, cardiomyopathy and myocarditis [6, 18-22]. Till to date there is scarcity of available published data regarding side effect profiles in local patients taking clozapine in Bangladesh. So, authors intended to observe pattern of distribution of diagnoses and the side effects profile of patients getting clozapine in a country like Bangladesh where there is still no national guidelines.

3. Methods

This cross sectional study conducted in the inpatient department of psychiatry, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from August 2016 to April 2017. Total 21 patients were included in the study. Prior the study authority was informed and informed written consent was taken from the respondents or legal guardians. The hospitalized patients getting clozapine were included in the study. Clozapine was started in accordance with the National Institute for Health and Clinical Excellence (NICE) guidelines. Researchers collected data with semi

structured questionnaire and preformed checklist by taking history (face to face interview), clinical examination and available laboratory investigations. The physical examination was done thoroughly including the vital signs, anthropometric parameters (height, weight and waist circumference) and other systems of the body. The considered available laboratory investigations were Complete Blood Count, CRP, Serum Creatinine and Urea, Liver enzymes, Blood glucose, Serum lipid profile, ECG, and chest radiograph. Data were analysed by Statistical Package for Social Science (SPSS) 16 version and Microsoft Excel Version 2007.

4. Results

4.1 Demography

The mean age of the respondents were 28.19 years (SD 1.19); age range were 15 to 60 years; 71.4% of the respondents were male, 52.4% were from rural background (Table 1), monthly income was more than 30000 BDT among 59.1% and rests earned lesser. Most of the patients were unemployed and students (28.6%, 23.8%). The remaining patient's profession were home maker, businessman, service holder and others (Table 1). Among the patients 28.6% were smoker and 50% of the patients consulted with traditional healer prior taking medical advice (Table 2).

Demographic Variable	**Frequency**	**Percentage**
Age in Years		
15-24	9	42.86
25-34	5	23.81
35-44	5	23.81
45-54	1	4.76
55-64	1	4.76
Sex		
Male	15	71.43
Female	6	28.57
Marital Status		
Married	7	33.33
Unmarried	11	52.38
Divorced	2	9.52
Widow	1	4.76
Habitat		
Urban	10	47.62
Rural	11	52.38
Occupation		
Unemployed	6	28.57
Student	5	23.81

Others	4	19.05
Housewife	2	9.52
Service	2	9.52
Business	2	9.52
Education		
Primary	1	4.76
Secondary	10	47.62
SSC (Grade 10)	4	19.05
HSC (Grade 12)	2	9.52
Graduate	2	9.52
Postgraduate	2	9.52

Table 1: Distribution of demographic variables of the respondents (n=21).

Disease Information	**Frequency**	**Percentage**
Diagnosis		
Schizophrenia	18	85.71
Bipolar Disorder	2	9.52
Tardive dyskinesia	1	4.76
First Contact for help seeking		
Traditional healers	11	52.38
Psychiatrist	7	33.33
General physician	3	14.29
Number of Antipsychotics prior to Clozapine		
At least 2 Antipsychotics	17	80.95
Others	4	19.05
Smoking		
Yes	6	28.57
No	15	71.43
Reported dose of response		
50 mg	3	14.29
75 mg	2	9.52
100 mg	4	19.05
200 mg	3	14.29
250 mg	1	4.76
300 mg	2	9.52
450 mg	1	4.76
500 mg	1	4.76
Non Responders	4	19.05
Dosing schedule		
Two divided dose	15	71.43
Once daily	6	28.57

Table 2: Distribution of diseases information of the respondents (n=21).

4.2 Clozapine therapy

66.5% of the patients were getting clozapine from 75-300 mg/day and rests were from 350-600mg/day. Regarding frequency of dose, 15 patients were getting two divided dose and 06 were getting single dose (Table 2). Among the study populations, 85.7% of respondents were found to have TRS, 9.5% were found to have TRBD and 4.8% were found to have TD (Table 2). About 81% of patients took at least two other antipsychotics in adequate dose and duration (Table 2). 12 patients responded at the dose of 50-200 mg/day, rest 5 responded at 250-500 mg/day (Table 2) and other 4 patients were clozapine resistant.

4.3 Side effects profile

Among the patients sedation (90.5%), hyper salivation (81%), constipation (81%), nausea (23.8%), nocturnal enuresis (23.8%), seizure (4.8%), hypertension (9.5%), and tachycardia (28.6%) (Table 3) were found as side effects. The side effects varied with the different dosage of clozapine. Seizure was found at 500 mg, hypertension was at 100mg. Side effects started with 25 mg of clozapine were sedation, hyper salivation, constipation, nausea, and tachycardia. Agranulocytosis, neutropenia, eosinophilia, thrombocytopenia, GERD, colitis, parotid swelling, raised liver enzyme, hepatic failure, pneumonia, pericardial effusion, carditis, cardiomyopathy, vasculitis, heat stroke, and stuttering were not found in the current study.

Side Effects	Frequency	Percentage
Sedation	19	90.48
Hypersalivation	17	80.95
Constipation	17	80.95
Tachycardia	6	28.57
Nausea	5	23.81
Nocturnal enuresis	5	23.81
Hypertension	2	9.52
Hypotension	1	4.76
Seizures	1	4.76

Table 3: Distribution of side effects of Clozapine therapy among the respondents (n=21).

5. Discussion

There is paucity of published data regarding soico demographic variations, diagnoses and clozapine side effects in Bangladesh. 50% of the study population initially consulted with traditional healer due to their primary illness and clearly suggests inadequate health literacy. But, it is found in previous research that health literacy is important in health outcome and lower health literacy results in poor health outcome [23]. At present there is no available national guideline or protocol regarding the use of psychotropics in Bangladesh. In the study place clozapine therapy

was given according to updated European guideline [6]. Clozapine therapy was given among the patients of TRS, TRBD and TD which is aligned with the evidence based psychiatric practice [3, 6, 24]. Though the effective therapeutic dose is 350 to 950 mg/day [6] in TRS, this study revealed that most of patients of TRS 64% (09) responded at 50-200 mg/day and remaining responded at 250-500 mg/day which indicates the lower effective dose than European population [6]. Failure to respond to at least two trials of dissimilar treatments, involving an adequate dose and duration is called TRBD [24]. Among the different options to treat TRBD, clozapine is an effective option [4, 24]. Other recommended treatment options for TRBD are calcium channel antagongist [25], quitiapine [26], combined Electroconvulsive Therapy (ECT) and clozapine [27, 28], clozapine [4, 29, 30], olanzapine [31], lithium and carbamazepine [32] and ECT [33, 34]. The study revealed that TRBD responded to clozapine at 100 mg/day along with sodium valproate which matches the findings reported by Arafat et al. in the same region [4]. TD is a clinical syndrome of iatrogenic origin due to antipsychotic drugs and presents with abnormal involuntary movements. It has been now the common practice to withdraw ongoing antipsychotic and use clozapine for treatment of TD [6]. Other than clozapine, highly selective vesicular monoamine transporter 2 inhibitor, tetrabenazine, valbenazine, high dose pyridoxine, bilateral Deep Brain Stimulation (DBS) are recommended options in TD treatment [35-39]. In this study clozapine given to a TD patient and was responded at 50mg/day which matches other evidences [6]. This study didn't observe any atypical or life threatening conditions like Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [40].

The study revealed common side effects of clozapine such as sedation, hyper salivation, constipation, nausea, nocturnal enuresis, seizure, hypertension, and tachycardia (Table 3) and severe life threatening side effects were not found. The phenomenon can be expected and explained by previous evidences and recommendations of following standard protocol of clozapine therapy.

6. Conclusion

This study replicates the previous findings of clozapine effectiveness in TRS, TRBD and TD. Social myths found to be a delaying factor to receive modern medical management of psychiatric morbidities. The results suggest that even in Asian community the side effects profile of clozapine therapy is quite similar to western part of globe. In future further study in large sample could be representative that can be useful in local evidence based psychiatric practice.

7. Conflict of interest

Authors having no conflict of interest.

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