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ORIGINAL ARTICLE

Reluctance in Clinicians to Start Clozapine Treatment: A Heavy Toll in Clinical Outcome in Schizophrenia

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ABSTRACT

Objective: Purpose of our study is to determine the frequency of treatment with clozapine among patients with treatment resistance schizophrenia.

Study Design: Cross sectional study

Place and Duration: Sughra Shafi Medical Complex Narowal. April 2020-October 2020

Methods: Total 23 patients of both genders had age 25-50 years were presented. All the patients had treatment-resistance schizophrenia and admitted to hospital for treatment.Only 4 patients were on clozapine while 19 patients were on other Antipsychotics. Patients were enrolled after taking informed written consent for detailed demographics. SPSS 22.0 was used to analyze all data.

Results: Among 23 patients, 17 (73.9%) were males and 6 (26.1%) cases were females.Mean age of the the patients was 34.16±8.30 years and had mean BMI 24.2±6.37 kg/m^2. Majority patients 15 (65.2%) had poor socio-economic status and 13 (56.5%) cases had urban residency. Only 4 (17.4%) patients received clozapine treatment. Psychiatristswere hesitating to provide clozapine among 19 (82.6%) cases. Reasons for hesitance to prescribe clozapine included concerns about major adverse effects and patients' lack of adherence, as well as difficulties in finding appropriate patients, service fragmentation, and a lack of familiarity with the drug.

Conclusion: Clozapine continues to be under prescribed for individuals with treatment-resistant schizophrenia owing to several hurdles relating to the physician, the system of care, and technology. In order to overcome these obstacles, it is suggested that prescriber expertise and training be enhanced, integrated care be implemented, and technology be used to provide continuous, real-time monitoring of blood tests.

Keywords: Treatment-resistance Schizophrenia, Clozapine, Complications, Antipsychotics

INTRODUCTION

Clozapine is a second-generation, dibenzodiazepine-based antipsychotic that is quite unusual. It is unlike any other antipsychotic since it interacts with many receptors, including dopamine, serotonin, adrenergic, histaminergic, and muscarinic [1, 2].

Multiple studies from all around the world have confirmed clozapine's efficacy. Clozapine not only reduced symptoms of psychopathology, but also improved patients' overall quality of life [3]. It is currently often used to treat a variety of mental diseases, such as treatment-resistant schizophrenia and manic depression. Tardivedyskinesia, severe psychotic depression, idiopathic parkinson's disease, huntington's disease, pervasive developmental disorder, autism in children, and intolerance to extrapyramidal symptoms are among the additional indications [4,5]. Studies have shown that clozapine can help reduce suicidal ideation, agitation, aggression, and hostility in people with schizophrenia. Reducing desire is another benefit in persons with schizophrenia who simultaneously use alcohol or drugs [6].

Because of the known risk for agranulocytosis, estimated at a prevalence of 1-2%, producers of clozapine products (now genericized in most countries) have instituted mandated monitoring systems to ensure that patients undergo routine blood tests prior to each dispensation. Patients should be instructed to begin treatment gradually and to keep their white blood cell (WBC) and absolute neutrophil (ANC) counts within a safe range (WBC count 3500/mm3 and ANC 2000/mm3) at all times [7]. That way, people who are at risk for agranulocytosis can be diagnosed and treated before the disease becomes fatal. Clozapine-related mortality and morbidity have been drastically cut thanks to the establishment of registries for the monitoring of haematological toxicity [8].

New "atypical" antipsychotic medications also became available in the 1990s (e.g., risperidone, olanzapine, quetiapine also identified as second-generation agents, SGAs). Hope for better compliance and Quality of Life (QoL) in individuals afflicted by schizophrenia was sparked by the development of these drugs, which sought to achieve effective treatments equivalent to clozapine without the haematological damage. Compared to FGAs, early investigations showed that SGAs were superior in many ways, including a reduced incidence of EPS, more effectiveness for positive, negative, and mood symptoms, enhanced tolerability, and better cognitive benefits [9]. High-Gain Strategies (SGAs) were extensively embraced around the globe despite their higher price tags [10,11]. Treatment-resistant schizophrenia is defined as not responding to two trials of any other antipsychotic medication; however, none of the newer SGAs could demonstrate superiority to clozapine, and many published clinical practise guidelines [12,13] have recommended that clozapine be prescribed to patients with this condition in the last decade (either FGA or SGA). In spite of these guidelines and the mountain of data supporting clozapine's efficacy, the drug's prescription appears to be low, delayed, and frequently preceded by efforts at polypharmacy therapy, for which there is little clinical evidence of efficacy [14,15].

MATERIAL AND METHODS

This cross sectional study was conducted at department of psychiatry of sughra shafi medical complex Narowal and comprised of 23 patients. Included patients those have history of schizophrenia. Patients with other psychiatric illness and those did not provide any written consent were excluded.

All 23 patients were interviewed extensively to collect socio-demographic data, and then given a full physical examination, which included measurements of height, weight, and other anthropometric variables. The modified Kuppuswamy scale was used to classify the respondents' socioeconomic backgrounds. Preexisting conditions, diagnosis, and information regarding all other psychoactive medications prescribed and all the inquests that were accessible with the physician were taken, recorded on a proforma, and results tabulated. This included a review of all available copies of prescriptions, data that resides, clinical and discharge summaries.

Information clozapine, such as when it was started, how much was taken, how long it took to work, and any side effects was recorded using a distinct semi-structured proforma. For the

purpose of documenting clozapine's adverse effects, the Glasgow antipsychotic scale was employed. Patients were questioned in their native tongue to ensure comprehension, and a separate checklist was used to document any unwanted effects that the scale failed to capture. Patients' treating psychiatrists were made aware of any adverse effects they experienced so that they may implement a treatment plan and monitoring schedule.

Patients were put on clozapine starting with 25mg/day and it was gradually increased were the period of two months upto 300mg/day clozapine. Regularly blood tests were taken daily to check blood levels.This research classified agranulocytosis as a neutrophil count of less than 500 cells/mm3, thrombocytopenia as a neutrophil count of between 500 and 1500 cells/mm3, leukopenia as a total white blood cell (WBC) count of less than 3500 cells/mm3, and leukocytosis as a WBC level of more than 11.0 cells/mm3. Two readings over 126 mg/dl for fasting glucose were diagnostic of type 2 diabetes, and readings over 140/90 mmHg for blood pressure were diagnostic of hypertension and hypertriglyceridemia was defined as a blood triglyceride level more than 150 mg/dl.All data was analysed using SPSS 22.0.

RESULTS

Among 23 patients, 17 (73.9%) were males and 6 (26.1%) cases were females.(figure-1)

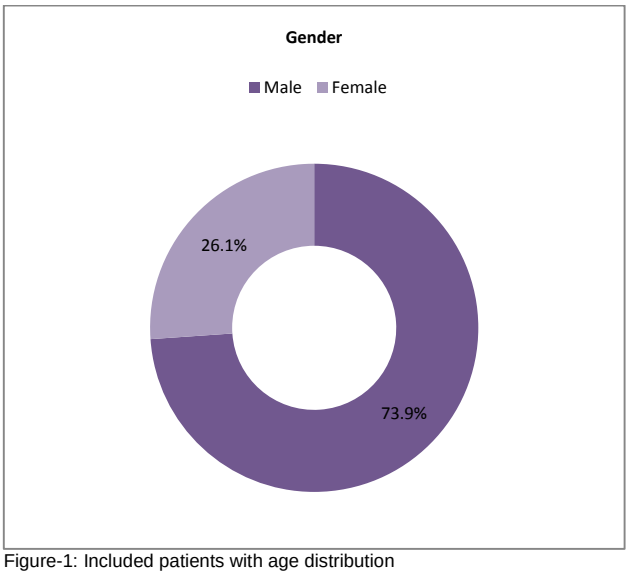

Figure-1: Included patients with age distribution

Mean age of the the patients was 34.16±8.30 years and had mean BMI 24.2±6.37 kg/m^2. Majority patients 15 (65.2%) had poor socio-economic status and 13 (56.5%) cases had urban residency. patients were married.(table-1)

Table-1: Demographics of enrolled cases

Variables	Frequency	Percentage
Mean age (years)	34.16±8.30	
Mean BMI (kg/m^2)	24.2±6.37	
Socio-economic status		
Poor	15	65.2
Middle/Upper	23	34.8
Place of living		
Rural	10	43.5
Urban	13	56.5
Marital Status		
Married	14	60.9
Unmarried	9	39.1

Among all cases, only 4 (17.4%) patients received clozapine treatment and these were aged between 40-50 years.(table-2)

Table-2: Frequency of reluctance and clozapine treatment

Variables	Frequency	Percentage
Clozapine Treatment		
Provided	4	17.4
Reluctance	19	82.6
Age of Patients received Clozapine		
41-45 years	1	4.3
45-50	3	13.04%

Reasons for hesitance to prescribe clozapine included concerns about major adverse effects and patients' lack of adherence, as well as difficulties in finding appropriate patients, service fragmentation, and a lack of familiarity with the drug.(table-3)

Table-3: Reasons of reluctance to provide clozapine

Variables	Frequency (19)	Percentage
Reason of Reluctance to Drug		
adverse effects	6	26.1
patients lack of adherence	3	13.04
difficulties in finding appropriate patients	4	17.4
service fragmentation	3	13.04
lack of familiarity with the drug	3	13.04

DISCUSSION

In spite of the heated and ongoing discussion over the relative safety and efficacy of FGAs and SGAs, clozapine has remained the drug of choice for the treatment of refractory schizophrenia throughout the past two decades (third-line agent). Additionally, it has been proposed that its usage (as a second string agent) might be advised sooner in those with chronic antagonism behaviour and suicidal ideation [16]. In fact, the FDA has given its stamp of approval for the treatment of repeated suicide attempts [17]. Even though further study is needed in the field of early onset schizophrenia and time to treatment response, clozapine's usefulness as a second line medication has recently been identified in a first-episode schizophrenic group [18].

The majority of our patients were men who were married, had jobs, were part of nuclear families, and were from lower socioeconomic backgrounds. Our study sample's demographics align with those found in prior research [19]. We found that treatment-resistant schizophrenia was the most prevalent reason for using clozapine. Early beginning of this condition is associated with lower life outcomes, including lower educational achievement, lower vocational skill acquisition, and lower social skill acquisition, all of which have negative effects on employment and marital stability [20]. Hospitalizations and drugs are significant contributors to the high costs connected with this ailment, which contributes to the deterioration of the economy as a whole due to the constant nature of therapy required by the patient [21]. Though treatment-resistant schizophrenia is associated with poor results, our research reveals that some individuals may be able to complete higher education with the support of clozapine if the drug is started early enough. Only 4 patients received clozapine treatment in our study and remaining were on other treatment.

The use of clozapine in our patients spans a wide range of conditions, from those that are resistant to treatment to those that combine movement disorders and psychosis, such as tardivedyskinesia. As has been disclosed in several studies [22], medicine schizophrenia was the most commonest cause for clozapine use in ours. Prescriptions for clozapine have followed the same pattern everywhere, with the drug being saved almost exclusively for the most difficult cases. According to research by S.W. Xu et al. [23], clozapine has been prescribed to Indian patients with schizophrenia who have shown intolerance to other antipsychotics or who have experienced serious side effects like neurogenicsymptomatology and tardivedyskinesia (TD).

Clozapine related adverse outcomes were hypotension, cardiomyopathy, sedation, dizziness, hypersalivation and

constipation in current study. Even though clozapine is widely regarded as the golden standard of treatment, its utilisation has lagged behind that which is suggested by professional practise standards. It has been determined that the relatively high incidence of neutropenia is a major factor in doctors being hesitant to prescribe clozapine; however, the close monitoring of White cell counts and Constituent assembly has just about completely abolished the chance of fatal agranulocytosis; recently, the frequency of blood tests has been simplified, and then once WBC counts and Offers a glimpse have been retained inside of average levels for one fy, blood samples are now only required once in every 4 weeks. [24]

There seems to be a consensus amongst practitioners that clozapine is a harmful medicine and that patients won't adhere to it or be open to considering it as a therapeutic option. Based on the data analysed for this analysis, it seems that the present low volume of clozapine usage contributes to the widespread yet unfounded misconceptions regarding this medication. If doctors don't think clozapine helps, they won't be likely to prescribe medication, which may start a vicious cycle. These findings corroborate those of a research by Stroup et al., which found that patients were more likely to start using clozapine if they lived in a region with both a history of heavy clozapine use and a high concentration of psychiatrists (more than 15 per 100,000 people). [25,26]

CONCLUSION

Clozapine continues to be under prescribed for individuals with treatment-resistant schizophrenia owing to several hurdles relating to the physician, the system of care, and technology. In order to overcome these obstacles, it is suggested that prescriber expertise and training be enhanced, integrated care be implemented, and technology be used to provide continuous, real-time monitoring of blood tests.

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