



Original Article

# Prevalence of agranulocytosis during treatment with clozapine in psychiatric hospitals in Mashhad, Iran

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## Abstract

**Introduction:** Clozapine is an atypical antipsychotic agent that is more effective than standard antipsychotic drugs in the treatment of patients with refractory schizophrenia. The main factor limiting its use is the risk of potentially fatal agranulocytosis. The aim of this study was to assess the prevalence of clozapine-induced agranulocytosis and other white blood cell disorders among patients in psychiatric hospitals of Mashhad.

**Materials and Methods:** This study analyzed the data of 210 patients received clozapine in Ibn-e-Sina and Hejazi hospitals in Mashhad during September 2012 to September 2013. In most cases hematologic monitoring was weekly for the first 18 weeks, then it changed to every month. The questionnaires included demographic factors such as age, gender, type of psychiatric disorder, duration of treatment, maximum dose of clozapine and concomitant antipsychotics were fulfilled through the patient's medical records. Data analyzed by descriptive tests, chi-square and exact Fisher test.

**Results:** The patients included 102 males and 108 females with the mean age of 38.3 years. The duration of clozapine treatment was one month (37.6%) and 1-3 months (36.2%) The maximal daily dose for 56.2% of patients was 150-299 mg/day. 60.4% received concomitant antipsychotics. No case of agranulocytosis was seen but the following transient hematologic dysfunctions were shown in 20.4% decrease of white blood cell, anemia (4.7%), eosinophilia (11.4%), thrombocytopenia (9.5%), leukocytosis (3.3%) and chronic leukocytosis (2.3%). There were no significance between white blood cell decrease and age, usage dose, concomitant use of other antipsychotics ( $P>0.05$ ), but the white blood cell reduction was more in women ( $P=0.01$ ) and there also was a significance between white blood cell decrease and treatment duration ( $P=0.011$ ). There was no case of agranulocytosis and mortality among leukopenic patients.

**Conclusion:** Considering the lack of agranulocytosis in this study, it is recommended to lengthen the intervals of hematologic monitoring in patients who are under treatment with clozapine in order to be easier and more economical.

**Keywords:** Agranulocytosis, Clozapine, Leukopenia, Psychotic disorders

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## Introduction

Clozapine is an atypical psychotic and a three rings derivation of benzodiazepine (1,2).

Apart from having conflict with dopamine binding to D1, D2, D3 and D5 receptors and light blocking effect on their receptors, it has high affinity for binding to D4 receptor (3-6).

It also acts as an antagonist for alpha adrenergic,

cholinergic, histaminergic and serotonergic receptors (3,6).

According to evidences the inhibitory effects of clozapine on the limbic dopamine receptors are higher than nigrostriatal dopamine receptors which can explain the lack of extrapyramidal complications (3,6) and the most important indication of clozapine includes treatment of schizophrenic patients with intolerable extrapyramidal complications (1,7,8) other usages were for reducing the risk of recurrent suicidal behavior in schizophrenic or schizoaffective patients (5), controlling of psychoses that are resistant to treatment resulted from Parkinson(5),

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treatment of tardive dyskinesia (5) and treatment of resistant form of bipolar mood disorder (5). Although clozapine is the most effective anti-psychotic for treatment of schizophrenia that has resistance to other forms of treatment, agranulocytosis is its most threatening side-effect which makes the usage of clozapine limited. Drug-induced neutropenia with absolute neutrophil count of less than  $1500/\mu\text{l}$  has been observed during treatment with second generation antipsychotics (clozapine, olanzapine, risperidone and quetiapine) (9). If the number of neutrophils is less than  $500 \text{ cells}/\text{mm}^3$  it is called agranulocytosis and if the number of granulocytes be less than  $1500 \text{ cells}/\text{mm}^3$  it is called granulocytopenia. Clozapine-induced neutropenia occurs in 4 to 5% of patients within 6 months after starting treatment and progress to agranulocytosis in 10% of neutropenic patients if the drug is continued (9). In 1975, 13 patients who were under treatment with clozapine in Finland got agranulocytosis and 8 of them dead because of secondary infections. This tragedy made clozapine to be on the list of black box (10,11). This report and others like that led to stop using clozapine or make some limitations for using this medicine in some countries and accurate hematologic monitoring in other countries. Demonstrating the efficient effect of clozapine on the patients with resistant and major Schizophrenia in 1990, it turned to be available again in Britain and United States but along with comprehensive circumstances about accurate WBC (White Blood Cell) monitoring (5).

Recent studies show that granulocytopenia and agranulocytosis both are reversible and they always do not have fatal side-effects (12,13). So, treatment with clozapine requires regular and accurate monitoring of leukocytes (14).

Prevalence of granulocytopenia is about 0.8-2% and it generally happens on the second or third month of treatment (between 4th-14th weeks). Agranulocytosis happens in 77% of patients within the first 18 weeks of Clozapine treatment (12,15). Among the patients who kept using medicine more than 3 month there was a significant decrease in weekly agranulocytosis. Subsequently, on the sixth month the cases of weekly agranulocytosis were 3 out of 1000 in a year and after six month this rate was going to be less but never got zero (1,3).

The mechanism of clozapine which leads to agranulocytosis is unknown yet but, old women and cachectic patients are more potential for that (4,5).

It seems that happening of this side-effect depends on the dosage. Apart from the fact that in most cases agranulocytosis happens at the early stages of

treatment, the treatment duration is not a factor to predict whether agranulocytosis happens or not (3,5,16).

A study of 11555 patients in 1991 showed that 73 of patients had agranulocytosis that for 2 of them it led to death resulted from infectious side-effects. After three months of treatment agranulocytosis was observed in 61 patients. Accumulative prevalence of agranulocytosis was 0.8% a year and 91% a year and half. Women were high risk for that and it went even higher as they got older (17).

In another study of 750 patients for 15 years in Budapest, granulocytopenia was observed in 7 patients (1%) and agranulocytosis in 2 (0.26%). Agranulocytosis was observed in 6th and 9th week of Clozapine treatment. By the way the blood examination had not shown any disorders in 5<sup>th</sup> and 8<sup>th</sup> week. These side-effects were reversible and not fatal in all cases (18).

Considering the efficient effect of clozapine in chronic schizophrenia treatment and the risk of getting agranulocytosis that may happen after using and according to this fact that there were no comprehensive studies in this field in Mashhad, we decided to investigate psychotics in Hejazi and Ibn-E-Sina hospitals.

### Materials and Methods

This study was done in faculty of medicine in Islamic Azad University of Mashhad. There were no economical or physical detriment to the patients and all the patients took part by their own interest. For keeping the personal information of the patients after collecting data, the name and last name of patients was converted to codes.

All the cases in this study were bedridden psychotics in Ibn-e-Sina and Hejazi hospitals, who had mental disorders. They have been studied for a year from September 2012 to September 2013. Among inpatients who were under treatment with medicine, 210 cases had expected conditions for our study. Questionnaires included age, sex, type of mental disorder, duration of treatment, the maximum dosage and the possible hematologic changes resulted from using other anti-psychotics and medicines at the same time have been filled by patients.

among the patients those who had been under treatment with this medicine for 1,2-3,3-6 and more than 6 months and had gotten CBC (Complete Blood Count) treatments weekly or biweekly at least at the first 18 weeks and also had had hematologic monitoring once a month were selected.

Expected conditions for entrance to studying:

1- Patient with no case history of hematologic and cardiovascular disease.

2- No past history of neutropenia or agranulocytosis resulting from clozapine or other medicines.

3- No usage of bone marrow inhibitory medicine in the same time.

Blood sampling was done as aforementioned intervals of about 2 cc by EDTA at each time and different factors were measured by Sysmexk21. For prove of hypothesis the  $\chi^2$  test with 95% assurance factors was used.

in addition to that for any cells of the chart that had value less than 5 in more than 25% or for 2+2 tables the Exact Fisher test and for other values the Exact test were used.

Observed hematologic alternations in this study after adaption with Sysmexk21 definitions were as follows:

- Agranulocytosis  
neutrophil count less than 500cell/mm<sup>3</sup>
- Minor leucopenia  
WBC: 3000-3500 cell/mm<sup>3</sup>
- Moderate leucopenia  
WBC: 2000-3000 cell/mm<sup>3</sup>
- Severe leucopenia  
WBC<2000 Cell/mm<sup>3</sup>
- Sudden decrease  
significant decrease of WBC about 3000 cell/mm<sup>3</sup> or even more than 3500 cell/mm<sup>3</sup>
- Gradual decrease  
gradual decrease about 3000 cell/mm<sup>3</sup> or even more within the three weeks

**Results**

After collecting data and analyzing them, the results are as follows:

Among 210 patients, 102 (48.6%) were men and 108 (51.4%) women. 12 (5.3%) were 20-39 years old, 86 (41%) 40-59 years old, 8 (3.8) more than 60 years old and 4 (1.9%) less than 20 years old.

The information of treatment duration, Clozapine dosage, and using other anti-psychotic in the same time are in Table 1.

**Table 1.** Treatment duration, clozapine dosage, and using other anti-psychotic in the same time

Variable	Frequency (%)
Treatment duration (month)	1 79 ( 37.6% )
	1-3 76 ( 36.2% )
	3-6 17 ( 8.1% )
	>6 38 (18.1% )
Maximum clozapine dosage	<150 mg 61 (29% )
	150-299 mg 118 ( 56.2% )

300-600 mg	31 ( 14.8% )
Other psychotic in the same time	Atypical 41 ( 19.5% )
	Typical 67 ( 31.9% )
	None 102 ( 48.6% )

170 patients were hospitalized at Ibn-e-Sina hospital and 40 patients at Hejazi hospital.

To recognize the reasons of hospitalization the results show that 58.6 persons of patients had schizophrenia, 27.6% bipolar disorder and 13.8% with other mental disorders.

The study showed that 43 (20.4%) patients had decrease in WBC but 167 (79.6%) patients did not have this decrease. The information of variety of decreased WBC is in Table 2.

**Table 2.** The frequency of decreased WBC in 210 inpatients by the type

Type of decrease	Minor leucopenia	Moderate leucopenia	Severe leucopenia	Gradual decrease	Sudden decrease	Total
Frequency (%)	8 (3.8% )	3 (1.42% )	1 (0.47% )	7 (3.33% )	24 (11.42% )	43 (20.4% )

Finally, there were no significant relations between decreased WBC and age ( $P=0.32$ ,  $\chi^2=2.78$ ) Clozapine maximum dosage ( $P=0.74$   $\chi^2=0.6$ ) and use of other anti-psychotics in the same time ( $P=0.14$ ,  $\chi^2=3.98$ ). Treatment duration and sex had significant relations with decreased WBC (Table 3).

**Table 3.** The frequency of decreased WBC by sex and treatment duration of 210 inpatients

Variable	Decreased WBC	Result
Sex	Men 13 (30.2% )	$P=0.01$ $\chi^2=7.47$
	Women 30 (69.8% )	
Treatment duration (month)	1 11 (25.6% )	$P=0.011$ $\chi^2=11.01$
	1-3 13 (30.2% )	
	3-6 4 ( 9.3% )	
	6< 16 (34.9% )	

In this study there were no cases of agranulocytosis. About 74.4% of patients who had had WBC decrease were cured spontaneously, 11.6% the daily dosage is decreased and only in 14% the treatment is stopped.

**Discussion**

The study was done on 210 patients, 170 patients in Ibn-e-Sina hospital and 40 patients in Hejazi hospital who were under treatment with clozapine. 58.6% had schizophrenia, 27.6% had bipolar disorder that both groups are main indication for clozapine.

The mean age was 38.3 years old that is approximately similar to 38 years old in study of 656 patients in Denmark (19).

60.4% of patients used other anti-psychotics in the same time that as there had not been enough information of that, we did not import them here. In a study (19) 35% of patients have used other anti-psychotics in the same time that shows the higher usage in our study.

The maximum dosage of clozapine was between 200-600 mg that shows that psychiatrists in Mashhad do not have tendency to increase the daily dosage of clozapine which may be the result of being concern about the side-effects like convulsion. Considering that the hematologic side-effects and agranulocytosis do not depend on dosage, so taking low dosage generally does not make any disorders to studying.

In a study by Peacock et al. (19) the average of clozapine dosage in women was 300mg/day and in men was 400 mg/day. Our survey shows that the general decrease in WBC were 12.7% in men and 28% in women that indicates a significant relation between sex and the incident of decreased WBC ( $P=0.01$ ) that means the decrease WBC count in women are more than men that is similar to different references that mention the higher prevalence of neutropenia and agranulocytosis in women (3,5,17). In our study the relation between decreased WBC and age, maximum dosage and using other anti-psychotics were not significant.

Different references mention that the decrease of WBC does not depend on maximum dosage of Clozapine (3,5,16) but they also mention that the aged people are high risk group for agranulocytosis (4,5).

The relation between the decreased WBC and Clozapine treatment was significant and it mostly happened at first three months and after six months of treatment. in another study (17) most cases of agranulocytosis (61 out of 73) also happened at the first three month The most of them were for the third month and only three cases happened after six months and one case after a year and half and the result was really similar to ours.

Finally, in contrast with (20) that 0.7% in the first year and (21) that 0.05% of under studied population had agranulocytosis, there were no cases

of agranulocytosis in our study. The possible reasons are as follows:

1- The presence of genetic factors: The prevalence of this disorder maybe is less in Iranian. The interfere of genetic factors in increase of agranulocytosis in Ashkenazi jews Who have some special types of HLA (DR4, DRw3, B38) has been demonstrated (17). The lower prevalence of agranulocytosis in our study may depend on ethnic and genetic factors. To prove this hypothesis, an organized study of the whole country is required.

2- In different studies and references it is mentioned that clozapine can result in reversible leukopenia and neutropenia and it might be the physician's caution and accurate monitoring which leaded to early diagnosis of leukopenia and neutropenia resulted in not having any agranulocytosis cases. Other references also mention that the diminution of WBC evaluating times may result in increase of agranulocytosis and death (3,5).

3- By a weak possibility the little mount of specimens even can be a reason for lacking of agranulocytosis in our study but, a study in Australia among 68 patients who had taken Clozapine, just one of them had agranulocytosis that make our third hypothesis less acceptable.

According to references we do not need to stop clozapine till the WBC count is not less than 2000. While in our study although we had one case of major leukopenia 6cases had been avoided taking Clozapine that shows the caution of our physicians.

Considering that mental patients mostly do not have medicine compliance finding information about the usage history was really hard and for chronic patients who usually do not aware of their problem seemed impossible although, we tried to find their first hematologic information by looking up to their previous dossiers.

Early release of many patients under permission of physicians or their own willing result in an obvious decrease of specimens. Although some patients had taken medicine for an appropriate duration they had not had an efficient hematologic monitoring that might be for several hospitalizations and taking medicine in the past that leaded them to be deleted from our list.

Most of the patients in Hejazi hospital use clozapine chronically but the access to their first dossiers were too hard and additionally going to remedial wards for several times was not possible considering lack of sufficient facilities. So, filling of many questionnaires of this group did not happen.

## Conclusion

Considering there were no cases of agranulocytosis and the fact that this condition mostly happens in women and is related to treatment duration, it is recommended to make a protocol of WBC screening

in patients who are under treatment with clozapine in order to decrease the necessity of regular expensive testing.

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