

# What Antipsychotic Medications and Risk Factors Are Associated With More Relapses in Chronic Schizophrenia Patients?

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## Abstract

**Background:** Schizophrenia is a chronic illness, with the majority of patients experiencing multiple relapses. Our aim is to survey the risk factors and antipsychotic medications associated with more relapses in schizophrenia patients.

**Methods:** The records of 251 schizophrenia patients who were adherent to their antipsychotic medications during the course of their illness were surveyed. The files were divided to two groups with regard to the number of admissions. The groups were compared regarding age, sex, education, marital status, place of living, family history, positive or negative symptom profile, substance abuse and the antipsychotic medications used.

**Results:** The patients of the two groups did not show any differences regarding demographic factors. The dominant antipsychotic (the antipsychotic used more than 50% of time during the course of illness) used in the two groups was risperidone without significant difference ( $P = 0.486$ ). Only substance abuse ( $P = 0.090$ ) and electroconvulsive therapy (ECT) administration ( $P < 0.001$ ) were shown to be different between the groups.

**Conclusions:** Antipsychotics were not revealed to have preventive effects for relapse. Less substance abuse was demonstrated to lessen the risk of relapse.

**Keywords:** Schizophrenia; Relapse; Risk factors; Antipsychotics

## Introduction

Schizophrenia is a chronic and disabling illness, with most of

the patients experiencing several relapses during the course of the illness [1]. Relapse, characterized by acute psychotic exacerbation, may have serious implications. For example, there is a risk of patients harming themselves or others, of destroying education or employment status and of further stigmatization of the illness [2]. A 5-year analysis of 11,291 patients with schizophrenia found a 13.4% re-hospitalization rate within 1 month, 38.9% within 1 year and 64.1% within 5 years [3]. According to a recent meta-analysis of 65 randomized trials, patients treated with antipsychotics experienced a psychotic relapse within 1 year in 27% of the cases [4].

Multiple factors contribute to increasing the risk of relapse. In a systematic review and meta-analysis of longitudinal studies it was shown that treatment noncompliance, substance abuse, carers' criticism and poorer premorbid functioning significantly increased the risk for relapses [5]. In another systematic review, male sex, unemployment, prior psychiatric admission, premorbid adjustment, childhood isolation, poor premorbid functioning, schizoid-schizotypal traits, and more severe negative symptoms were reported as risk factors for relapse [6]. Several studies have found that the most common risk factor was antipsychotic medication discontinuation [7-9]. Taking the medication on a daily base, emergence of side effects and not having positive attitude toward medications are main reasons to discontinuing treatment [10, 11].

In our review of literature, we did not find any study surveying the association between antipsychotic medications and relapse in chronic schizophrenia patients. In this research, our aim is to survey the risk factors and antipsychotic medications that are associated with more relapses in chronic schizophrenia patients.

## Patients and Methods

This retrospective study would survey the demographic and clinical factors and also the antipsychotic medications associated with more relapses in patients with diagnosis of schizophrenia.

## Patients

The patients were diagnosed to have schizophrenia according to

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**Table 1.** Demographic Characteristics of the Patients

	Patients with 3 or < 3 admissions	Patients with > 3 admissions	P value
Age (mean)	37.82	44.01	0.42
Female (%)	81 (45%)	41 (41%)	0.78
Married (%)	56 (28.3%)	35 (36.5)	0.108
High school diploma (%)	69 (34.8%)	37 (38.5%)	0.374
Rural resident (%)	48 (24.2%)	21 (21.9%)	0.653
Positive FHx of schizophrenia (%)	55 (27.8%)	27 (28.1%)	0.95

FHx: family history.

Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria by a board-certified psychiatrist through a clinical interview. Inclusion criteria were: 1) Course of illness for at least 10 years; 2) Adherence to antipsychotic medications during the course of illness; and 3) Having at least one episode of hospitalization in psychiatry ward. The patients were excluded if: 1) They had any other psychiatry or medical disturbances; 2) They had used clozapine or any injectable antipsychotics during the course of illness; 3) They had relapses without hospital admissions; and 4) Their hospital files were not complete.

### Procedure

All the records of the patients with diagnosis of schizophrenia that had been admitted in Ebnesina Psychiatry Hospital in Shiraz, Iran from February 2015 to February 2020 were surveyed. The files that met with our inclusion criteria were selected for study. The patients were divided in to two groups: those with a history of three or less than three admissions and those with history of more than three admissions. The two groups were compared regarding demographic and clinical characteristics and also the antipsychotic medications used.

### Medical ethics

The study was approved by the ethics committee of Shiraz University of Medical Sciences that adheres to the Declaration of Helsinki Ethical Principles for Medical Research, 1964.

### Data analysis

The data were analyzed using SPSS (version 23). The clinical and demographic characteristics of the two groups were com-

pared using Chi-square and Mann-Whitney tests. P values less than 0.5 were considered significant.

## Results

The files of 1,210 schizophrenia patients were studied. A total of 251 files were selected according to our inclusion and exclusion criteria to be surveyed. Of the 251 files, 166 patients (67.3%) had history of three or less than three admissions and 85 patients (32.7%) had history of more than three admissions.

### Demographic characteristics

The patients' age, sex, marital status, education level, place of living and family history were studied. The two groups' characteristics were compared. Table 1 depicts the patients' demographic characteristics. The patients with more relapses did not differ significantly with those with less relapses regarding demographic factors.

### Clinical characteristics

There was no significant difference between the two groups with regard to clinical symptoms profile (positive or negative). The only studied factors that differed significantly between the two groups were electroconvulsive therapy (ECT) administration and substance abuse. Table 2 depicts the comparison of clinical variables between the two groups.

### The antipsychotic medications

The two groups were compared regarding the dominant (the

**Table 2.** Clinical Characteristics of the Patients

	Patients with 3 or < 3 admissions	Patients with > 3 admissions	P value
With negative symptoms (%)	28 (14.1%)	12 (12.5%)	0.72
ECT administered (%)	61 (30.8%)	74 (77.1%)	0.001
Substance abuse (%)	65 (32.8%)	41 (42.7%)	0.09

ECT: electroconvulsive therapy.

**Table 3.** Dominant Antipsychotic Medications Used by the Patients

	Patients with 3 or < 3 admissions	Patients with > 3 admissions	P value
Risperidone	78 (46.9%)	37 (41%)	0.486
Olanzapine	38 (22.8%)	22 (24.4%)	0.685
Quetiapine	27 (16.2%)	11 (12.2%)	0.437
Aripiprazole	14 (8.4)	8 (9%)	0.846
Perphenazine	9 (5.4%)	7 (7.8%)	0.421

antipsychotic used more than 50% of time during the course of illness) antipsychotic medications used. Table 3 shows the antipsychotic dominantly used by patients of the two groups. Risperidone was the most common antipsychotic used in both groups without significant difference ( $P = 0.486$ ). Overall, there was no any difference between the two groups with regard to the antipsychotics used dominantly.

## Discussion

Our study revealed that the schizophrenia patients with more relapses did not have any difference with those with less episodes regarding sex, marital status, educational achievement, place of living and positive family history. Both groups also did not differ in the antipsychotic regimen treatment. Among other clinical characteristics studied, the patients with more relapses had received more ECT treatment and had more history of substance abuse.

Medication nonadherence has been reported to be the most important factor contributing to relapse in schizophrenia patients [8-12]. In a prospective, 5-year follow-up of first-episode psychosis patients, it was found that the most common risk factor by far was antipsychotic medication discontinuation [1]. In this study, we included patients that had a period of 10-year adherence to their antipsychotic medication. In this way, we tried to survey other factors contributing to relapse in schizophrenia patients.

Several studies have indicated that relapse reflects a period of disease progression in so far as patients may not return to their previous level of function and treatment refractoriness may emerge [13, 14]. Furthermore, these studies mention that more relapses indicate disease progression with poorer function and more disabilities. In one study, it was concluded that 80% of patients with schizophrenia were judged to have deteriorated over time in a 7-year follow-up study, and the degree of deterioration was significantly correlated with the number of relapses that patients experienced [15]. On the other hand, there are evidences to suggest that disease progression does not occur as a consequence of relapse. Wiersma et al reported that patients' symptoms rapidly returned to baseline with resumption of antipsychotic medication shortly after recurrence of psychotic symptoms in five out of six patients, regardless of which episode it is [16]; McGlashan concluded in his review article that active psychosis exacerbation is not essentially neurotoxic and would not cause brain degeneration [17]. Our results revealed that patients with more relapses were not associated with lower educational achievement or lower social functioning.

In our study, patients in both groups did not differ regarding sex. In contrast, Porecchi et al in their study found that male gender is a non-modifiable risk factor contributing to more relapses [18]. Bowtell et al in their review study also detected that some authors have concluded male gender to be associated with more relapses [6].

Positive family history was not associated with more relapse in our patients. Similarly, Bowtell et al in their systematic review concluded that positive family history would not predict more relapses in schizophrenia patients [6].

Another demographic factor that was surveyed in our study was the place living (rural/urban). Usually living in cities demands higher functioning and is associated with more stress. Due to higher expectations from the patients in urban area, carers' criticism is higher in urban area than in rural places. Carers' high demand and criticism have been found to be associated with more relapses [6, 18, 19]. However, we did not find any association between place of living and rate of relapses.

Among clinical factors studied, we observed that abuse of substance and ECT administration were more common in the group with more relapses. In line with our findings, some other studies also reflect the association between substance abuse and risk of relapse in schizophrenia patients [6, 16, 18, 20]. In a study on Iranian psychiatry patients taking ECT, it was shown that ECT is usually considered in more chronic and refractory schizophrenia patients [21]. This may justify the more ECT administration in the patients with more relapses in our study.

Some previous studies have found that the negative symptom dimension produces higher relapses compared to positive symptom profile [6]. However, Hafner concluded in his review study that positive symptom profile produces the highest number of relapses and the shortest duration of exacerbations [22]. In our study, symptom presentation profile did not differ between the two groups.

In this survey, we found that our patients were using risperidone (44.45%), olanzapine (23.6%), quetiapine (14.2%), aripiprazole (8.7%) and perphenazine (6.6%) as their dominant medication (more than 50% of time during the course of illness). The two groups did not differ significantly regarding the antipsychotic medication used dominantly during the course of the illness. It implicates that none of the antipsychotics have protective effect for relapse.

## Limitations

The first limitation is that our research is a retrospective one.

So some information may have been missed. Second, we just surveyed some demographic and clinical factors. Maybe other factors that we have missed could have important implications. Third, the research has been conducted in one hospital with limited number. Larger studies with multicenter involved would yield better results.

## Conclusions

We found that the schizophrenia patients with more relapses did not have any difference with those with less episodes regarding sex, marital status, educational achievement and positive family history. Antipsychotic medications did not show any preventive effect for relapse. Less substance abuse was revealed to reduce the risk of relapse.

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## Conflict of Interest

None to declare.

## Informed Consent

All patients provided written informed consent to participate in the study.

## Author Contributions

All the authors were involved in designing the method of this research and also contributed to carrying it out. Dr. Arash Mowla wrote the paper and submitted it to the journal.

## Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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