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Side Effects of Clozapine Treatment in Patients with Schizophrenia and Schizoaffective Disorder and Their Role in the Discontinuation of Treatment

Klozapin Tedavisi Alan Şizofreni ve Şizoafektif Bozukluğu Olan Hastaların Bildirdiği Yan Etkiler ve Yan Etkilerin Tedavi Sonlandırılmasına Etkisi

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ABSTRACT

Objectives: Clozapine is an effective atypical antipsychotic that has been successfully used in the treatment of schizophrenia and schizoaffective disorder, but its utilization is restricted due to the side effects. We aimed to investigate the side effects reported by patients using clozapine and their role in the cessation of the treatment.

Methods: In our study, the follow-up charts and admission files of patients with schizophrenia and schizoaffective disorder who were followed up regularly at outpatient clinics were reviewed retrospectively. 246 patients who had received or are currently taking clozapine were identified. The sociodemographic and clinical features of the patients, reported side effects, and the reasons for discontinuation were recorded.

Results: The most frequently side effects reported by the patients were sedation (35.6%), hypersalivation (27.9%), weight gain (19%), incontinence (8.1%), obsessive–compulsive symptoms (6.5%), seizure-myoclonus (4.9%), orthostatic hypotension (4.5%), leukopenia (3.6%), sexual side effects (1.2%), and constipation (0.8%). Clozapine treatment was terminated in 26.6% of the patients due to non-adherence to medication (35.4%), inadequate effect/side effect ratio (13.8%), ineffectiveness (12.3%) leukopenia (9.2%), seizures (7.7%), incontinence (6.2%), sedation (6.2%), obsessive–compulsive symptoms (3.1%), weight gain (3.1%), hypersalivation (1.5%), and orthostatic hypotension (1.5%). When the reasons for discontinuation were analyzed, it was determined that failure to provide sufficient effect and irregular use were significantly higher in patients who have a history of more suicide attempts

Conclusion: Side effects of clozapine treatment are common. Approximately one-quarter of patients receiving clozapine discontinued the treatment due to intolerance of side effects, non-adherence to treatment, or failure to provide sufficient effect. In patients with a worse course since the onset of the disease, treatment discontinuation due to insufficient efficacy and irregular use was higher.

Keywords: Clozapine; schizoaffective disorder; schizophrenia; side effect.

ÖZET

Amaç: Klozapin özellikle tedaviye dirençli şizofreni ve şizoafektif bozukluk tedavisinde kullanılan bir antipsikotik olup, yan etkileri nedeniyle kullanımı kısıtlanmaktadır. Çalışmamızda, klozapin kullanan hastaların bildirdikleri yan etkilerin ve bu yan etkilerin tedavinin kesilmesindeki rolünün araştırılması amaçlandı.

Yöntem: Çalışmamızda, hastanemizin psikiyatri polikliniklerinde şizofreni ve şizoafektif bozukluk tanılarıyla izlenen hastaların dosyaları retrospektif olarak incelendi. Geçmişte veya halen klozapin kullanmakta olan 246 hastanın bildirdiği yan etkiler ve eğer klozapin kesilmişse kesilme nedenleri ile hastaların sosyodemografik özellikleri, klinik özellikleri, bildirilen yan etkiler ve tedaviyi bırakma nedenleri kaydedildi.

Bulgular: Klozapin kullanılan hastalarda en sık bildirilen yan etkiler; sedasyon (%35,6), hipersalivasyon (%27,9), kilo artışı (%19), inkontinans (%8,1), obsesif kompulsif belirtiler (%6,5), nöbet-miyokloni (%4,9), ortostatik hipotansiyon (%4,5), lökopeni (%3,6), cinsel yan etkiler (%1,2) ve konstipasyondu (%0,8). Hastaların %26,6'sının klozapin tedavisinin kesildiği tespit edildi. Tedavinin kesilme nedenlerinin; %35,4'ünde düzensiz kullanım, %13,8'inde etki/yan etki oranının yetersiz olması, %12,3'ünde etkisizlik, %9,2'sinde lökopeni, %7,7'sinde nöbet, %3,1'inde kilo alımı, %6,2'sinde inkontinans, %6,2'sinde sedasyon, %3,1'inde obsesif kompulsif belirtiler, %1,5'inde hipersalivasyon ve %1,5'inde ortostatik hipotansiyon olduğu belirlendi. Klozapin tedavisinin kesilme sebepleri araştırıldığında; intihar girişimi sayısı fazla olan hastalarda düzensiz kullanım ve yeterli etkinin sağlanamaması nedeniyle ilaç kesiminin anlamlı olarak yüksek olduğu saptandı.

Sonuç: Klozapin tedavisi, hastaların yaklaşık dörtte birinde yan etkiler, düzensiz kullanım veya ilacın belirgin bir yararının görülmemesi nedeniyle sonlandırılmaktadır. Baştan beri olumsuz gidiş gösteren hastalarda klozapinin yanıtsızlık nedeniyle kesilmesi daha sıktır. Hekimlerin yan etkilerle etkin ve erken mücadele etmek konusunda farkındalığının artması, klozapin tedavisinin kullanılma oranlarının artmasına katkı sağlayacaktır.

Anahtar sözcükler: Şizofreni; şizoafektif bozukluk; klozapin; yan etki.

Clozapine was the first discovered atypical antipsychotic drug and has a unique efficacy profile in the treatment of psychotic disorders with its multiple receptor interaction. Approximately, one-third of schizophrenia patients do not respond adequately to two different antipsychotics despite appropriate dose, duration, and treatment compliance, and current international treatment guidelines recommend clozapine as the gold standard treatment in patients with treatment-resistant schizophrenia.[1,2] Studies in the literature have shown that it is effective on short- and long-term positive and negative symptoms, especially in treatment-resistant schizophrenia (TRS), increases the functionality and quality of life of patients, reduces rates of hospitalization up to 72%, is associated with a decrease in mortality, suicide, and aggression rates, and limits comorbid substance-use disorders.[3-8] In addition, since clozapine has a low risk of causing extrapyramidal symptoms unlike other antipsychotics, it is also recommended in Parkinson's psychosis and drug-induced tardive dyskinesia.[9,10]

While the efficacy of clozapine is well known by clinicians, concerns about possible side effects limit its common use. As it is known, clozapine may cause central, autonomic, cardiovascular, gastrointestinal, and hematological side effects. The study conducted by the British Clozapine Study Group reported that hypersalivation was the most common side effect (54%), followed by sedation (46%), constipation (44%), weight gain (11%), and epileptic seizures (9%).[11] In addition, fatigue, urinary incontinence, agranulocytosis, neutropenia, tachycardia, diabetes, metabolic syndrome, hypertension, orthostatic hypotension, electrocardiogram and electroencephalogram changes, myocarditis, and obsessive–symptoms are other reported side effects.[12] In order to be able to notice these side effects and keep them under control, patients should be questioned in this context at certain intervals during follow-up and their laboratory and physical measurements should be recorded.

Compliance with treatment is an important issue in patients with psychotic disorders. Although discontinuation rates of clozapine treatment is low compared to other antipsychotics, 40% of patients terminate clozapine treatment within the first 24 months.[13,14] Treatment discontinuation substantially results in rapid worsening, increased obligatory treatment, rehospitalization, and reduced functionality.[13] Risk factors associated with the cessation of treatment were found to be starting clozapine at an advanced age, black African/Caribbean race, and substance abuse, and it was reported that treatment was discontinued in more than half of the patients (56.3%) due to side effects.[14] When the side effects that may arise are known and questioned by the clinicians, the compliance of the patients to this efficient treatment that may be enhanced.

In our study, we aimed to investigate reported side effects of clozapine by patients with the diagnosis of schizophrenia and schizoaffective disorder and their role in the termination of treatment. Our hypothesis is that most important reason for discontinuing treatment may be manageable side effects. Our results will contribute to the literature by providing clues to ensure the continuity of well-being of patients who benefit from clozapine, with the clinicians' early recognition of possible side effects and their intervention.

Methods

This study is a retrospective, descriptive study aiming to describe the side effects reported by patients using clozapine who are being followed up with the diagnosis of schizophrenia and schizoaffective disorder in the Psychotic Disorders Unit of the Psychiatry Department of Istanbul Faculty of

Medicine and to reveal the role of these side effects in discontinuing treatment. The inclusion criteria of the study were to meet the diagnostic criteria for schizophrenia or schizoaffective disorder according to the DSM-IV (American Psychiatric Association-APA 1994) diagnostic criteria, to continue regular follow-ups, to have complete treatment records, and to be still using clozapine or to have stopped using clozapine before. The files of 1500 patients diagnosed with schizophrenia or schizoaffective disorder were scanned, and 246 patients who met the inclusion criteria were included in the study. Of these patients, 100 were followed up in the Psychotic Disorders Unit, 136 in the General Outpatient Clinic, and 10 in the Mood Disorders Unit. Approval for the study was obtained from the Istanbul Faculty of Medicine Clinical Research Medical Ethics Committee at its meeting numbered 16 on September 30, 2016.

Sociodemographic information, diagnosis and duration of the disease, psychopharmacological treatments and their duration, number of hospitalizations, electroconvulsive therapy (ECT), and suicide attempts, whether they meet the criteria for TRS, the reason for starting clozapine and duration of the clozapine treatment, level of response to clozapine treatment according to the physician and family, reported side effects, and if the treatment was terminated, the reason was recorded in the patient information forms from the outpatient follow-up and hospitalization files of the patients.

For the diagnosis of TRS, although at least two antipsychotic drugs were used at an equivalent dose of ≥400–600 mg/day chlorpromazine for 6 weeks, it was accepted that there was no period of good functionality without significant improvement in symptoms.[15] The improvement criteria were accepted as having a total score of ≥45 on the Brief Psychiatric Rating Scale (BPRS), which was recorded regularly during follow-up, and having at least 2 of the 4 items of the same scale related to positive psychotic symptoms being ≥4 points. BPRS is a semi-structured 18-item scale developed by Overall et al.[16] to measure the severity and variation of psychotic and some depressive symptoms in schizophrenia and other psychotic disorders. The validity and reliability study of the Turkish version was performed by Soykan.[17]

Statistical Analysis

Statistical analyses were performed using SPSS 16.0. The conformity of the variables to the normal distribution was investigated with the Kolmogorov–Smirnov test. Numerical variables were presented as mean±standard deviation. Categorical variables were presented with n (%) values. The Kruskal–Wallis test was used for comparisons of more than two independent groups, and the Mann–Whitney U-test was used for pairwise independent group comparisons to evaluate the predictors of discontinuation of treatment. A value of $p<0.05$ was accepted for statistical significance.

Results

In our study, the file records of 246 patients who were followed up in our clinic and met the inclusion criteria were examined. 66.3% of the patients were male, and the mean age was 36.7±11.1 years. 198 (80.5%) of the patients were single, 11.4% were married, and 8.1% were divorced/widowed. Of the patients, 79.7% were unemployed or low-functioning housewives, 13.0% were employed, 2.8% were functional housewives, and 4.5% were students. The mean duration of education was 10.8±3.5 years. 44.7% of the patients were smokers and 94.3% had no history of alcohol or substance abuse.

Considering the clinical characteristics of the patients, 232 patients were diagnosed with schizophrenia and 14 with schizoaffective disorder, and the mean disease duration was 14.3±8.04 years. 27.7% of the patients had at least one suicide attempt (56 before clozapine, 7 after clozapine), 34.8% of them had ECT in the past. The mean duration of clozapine was 54.2±56.6 months, the clozapine dose ranged from 75 to 1000 mg, and the mean dose currently used was 340.19±148.2 mg/day. 60.6% of the patients were using clozapine along with other antipsychotics, 40.5% were using mood stabilizers or antidepressants, and 23.5% were using antiepileptic drugs. Clozapine was started in 74% of the patients for TRS, 9.7% for intolerance to other antipsychotics, 6.5% for impulsivity, and 9.7% for other reasons. Clozapine was started on average 27.1±30.5 months after meeting the TRS criteria. Before clozapine, 6.9% used typical antipsychotics and 14.6% used atypical antipsychotics above the recommended dose in guidelines. Sociodemographic and clinical characteristics of the patients are shown in Table 1.

According to the subjective evaluations of the families of the patients, 2.8% of the patients did not benefit at all from clozapine, whereas 8.9% benefited minimally, 32.3% moderately, and 41.7% advanced. The treating physician, on the other hand, was of the opinion that 2% of the patients did not benefit at all, 10.9% had minimal, 37.6% moderate, and 38% advanced benefits.

Table 1. Sociodemographic and clinical characteristics of patients (n=246)

	n (%)
Gender	
Woman	83 (66.3)
Male	163 (33.7)
Marital Status	
Single	198 (80.5)
Married	28 (11.4)
Divorced/widowed	20 (8.1)
Operating Status	
None/nonfunctional housewife	195 (79.6)
Student	11 (4.4)
Paid worker/functional housewife	39 (16
Disease	
Schizophrenia	232 (94.3)
Schizoaffective disorder	14 (5.7)
Mean±SD	
Age (years)	36.7±11.09
Education (years)	10.80±3.54
Duration of illness (years)	14.3±8.04
Duration of clozapine treatment (months)	54.2±56.6
Clozapine dose (mg/day)	340.19±148.2
Duration between time to meet TRS criteria and start of clozapine (months)	29.3±30.5

n: number; SD: Standart deviation.

Considering the side effects, 35.6% of the patients under clozapine treatment reported sedation, 27.9% hypersalivation, 19% weight gain, 8.1% incontinence, 6.5% obsessive–compulsive symptoms, 4. 9% seizure myoclonus, 4.5% orthostatic hypotension, 3.6% leukopenia, 1.2% sexual side effects, 0.8% constipation, and 6.9% other side effects (Table 2).

Table 2. Side effects reported in clozapine treatment

	n (%)
Sedation	88 (35.6)
Hypersalivation	69 (27.9)
Weight gain	47 (19)
Incontinence	20 (8.1)
Obsessive-Compulsive Symptoms	16 (6.5)
Seizure-Myoclonia	12 (4.9)
Orthostatic Hypotension	11(4.5)
Leukopenia	9 (3.6)
Sexual Side Effects	3 (1.2)
Constipation	2 (0.8)
Other	17 (6.9)

n: number.

Hypersalivation has been reported frequently in those using clozapine with other antipsychotics (p=0.05) and those taking a higher mean maximum clozapine dose (p=0.02). Constipation (p=0.048) and orthostatic hypotension were more common in women (p=0.006), leukopenia in patients with a diagnosis of schizoaffective disorder (p=0.016), and obsessive–compulsive symptoms were more common in those using clozapine for a longer time (p=0.038). Clozapine treatment was terminated in 26.6% (n=65) of the patients either by themselves or by their physician. The mean duration of clozapine use in patients whose clozapine treatment was discontinued was 29.39±4.67 months, and the treatment of 27.7% of the patients was discontinued within the first 6 months, and the treatment of 55.4% after 1 year. When the reasons for discontinuation of the early period (first 1 year) and those who were stopped later were compared, no significant difference was found between the groups. When we compare the clinical features of patients who stopped clozapine treatment with those who continued, the rates of prior ECT (p=0.001), previous combined antipsychotic use (p=0.017), meeting the TRS criterion (p=0.021), total number of hospitalizations (p=0.001), the number of hospitalizations at 1 year before (p=0.008), and 1 year after clozapine (p=0.000) were higher.

Considering the reasons for the discontinuation of clozapine, patients' treatment was terminated due to noncompliance (35.4%), insufficient effect/side effect ratio (13.8%), ineffectiveness (12.3%), leukopenia (9.2%), seizures (7.7%), incontinence (6.2%), sedation (6.2%), obsessive–compulsive symptoms (3.1%), weight gain (3.1%), hypersalivation (1.5%), and orthostatic hypotension (1.5%) (Table 3). These

Table 3. Reasons for discontinuation of clozapine treatment

	n (%)
Irregular use	23 (35.4)
Insufficient effect/side-effect ratio	9 (13.8)
Ineffectiveness	8 (12.3)
Leukopenia	6 (9.2)
Seizure	5 (7.7)
Sedation	4 (6.2)
Incontinence	4 (6.2)
Weight gain	2 (3.1)
Obsessive-compulsive symptoms	2 (3.1)
Orthostatic hypotension	1 (1.5)
Hypersalivation	1 (1.5)

n: number.

reasons were grouped under three groups as the patient quitting the drug on his own as a result of irregular use (35.3%), intolerance to medical side effects (37.5%), and insufficient effect (26.1%) and the factors that could affect these were investigated. While there was no significant relationship between clinical and sociodemographic data in those who discontinued treatment due to intolerance to side effects, the number of suicide attempts (p=0.026) was significantly higher in patients whose treatment was disrupted due to irregular use and inadequate response.

Discussion

In our study, the most common side effects reported by 246 patients using clozapine with the diagnosis of schizophrenia and schizoaffective disorder were sedation, hypersalivation and weight gain, and incontinence, obsessive–compulsive symptoms, seizure-myoclonus, orthostatic hypotension, leukopenia, sexual side effects, and constipation. Clozapine treatment was discontinued in a quarter of the patients, and most of them were due to intolerance of side effects and irregular use, consistent with our hypothesis.

Studies have reported that clozapine treatment in patients with schizophrenia and schizoaffective disorder is effective in the short and long term, especially in positive symptoms, and reduces impulsivity along with negative and cognitive symptoms.[18] In our study, three-quarters of the patients benefited from the treatment according to their families and physicians. This utility was associated with primarily positive symptoms, negative symptoms, and impulsivity, consistent with the literature.[18]

Although clozapine is a highly effective atypical antipsychotic, due to its potentially fatal side effects and the requirement for regular blood monitoring, clinical indications are limited to TRS, recurrent suicide attempts in patients with schizophrenia and schizoaffective disorder, and patients with severe late dyskinesia who cannot tolerate the side effects of other antipsychotics.[19] In our patient group, the majority of clozapine treatment was started due to resistance to treatment, and other reasons were found to be intolerance to other antipsychotics and impulsivity. Although it is the only recommended treatment for TRS in studies, clinicians delay the initiation of clozapine treatment for an average of 47.7 months–5 years, even after meeting the criteria for TRS due to side effects and compliance problems.[20] When the past antipsychotic treatments given in our patient group were examined, it was found that the patients started using clozapine 27.1±30.5 months on average after meeting the TRS criteria, and approximately one-fourth of them used typical and atypical antipsychotics in higher doses than the recommended dose in the current guidelines before clozapine. The fact that our study sample consisted of patients who applied to a university clinic and followed up from specialized outpatient clinics for psychotic and mood disorders may explain the shorter duration than the reported ones in recent studies.

In the literature, there is a large amount of data on the side effects seen in patients with schizophrenia and schizoaffective disorder receiving clozapine treatment. Yusufi et al.[21] reported that 77% of patients reported at least one side effect when questioned, the most common one was sedation, and hypersalivation and sexual side effects were reported in

Table 4. Possible predictors of the main causes of discontinuation of clozapine

	Irregular use Mean±SD	Side effects Mean±SD	Failure to achieve sufficient effectiveness Mean±SD	p
Age	37.88±11.27	35.9±8.68	39.06±9.86	0.742
Education	10.47±3.64	12.4±2.81	12.0±3.42	0.156
Number of suicides	0.70±1.26	0.15±0.48	0.53±0.63	0.026
Duration of illness	13.9±8.05	14.0±5.86	18.0±6.36	0.221
Duration of use of clozapine	24.23±27.40	22.80±36.3	39.1±43.01	0.252
Maximum dose of clozapine	388.2±128.12	323.7±170.8	443.3± 237.4	0.290
Number of typical APs used before clozapine	1.11±1.31	0.40±0.59	1.40±1.63	0.072
Number of atypical APs used before clozapine	1.94±1.44	2.00±1.16	1.60±1.45	0.452
Total number of APs used (in sufficient dose and time) before clozapine	3.05±1.59	2.40±1.18	3.00±1.77	0.696

n: Number; SD: Standard deviation.

more than half of the patients. Breier et al.[22] found hypersalivation in the vast majority of patients and sedation and orthostatic hypotension in more than one-third. In a recent study in our country, the most common side effects were found to be hypersalivation, fatigue, sedation, constipation, followed by enuresis, dizziness, palpitation/tachycardia, and blurred vision.[23] In our study, the most common side effects were sedation, hypersalivation, and weight gain, and the frequency of the detected side effects was generally lower than the studies in the literature. Since our study was based on a retrospective review of the outpatient clinic files, the data were consisted of the side effects that physician questioned during the standard outpatient clinic interview or that the patient/relative reported spontaneously. The fact that side effects were not completely questioned, especially in the general outpatient clinic, may be a possible reason for the low rates.

When the factors that play a role in the occurrence of side effects were investigated separately for each side effect, no significant relationship was found with variables such as sedation, leukopenia, enuresis, and seizures and age, gender, disease duration, clozapine dose, and duration. However, the maximum dose of clozapine was found to be significantly higher in patients with frequent hypersalivation, and it was found that hypersalivation tended to be more common in patients who used clozapine with additional antipsychotics. Consistent with the data in studies about the increase in hypersalivation with clozapine dose and drug interactions, this finding suggests that it is important to avoid adding another antipsychotic to clozapine, unless it is necessary, in terms of reducing side effects.[24] In addition, recent studies have shown that the prevalence and severity OCD symptoms that occur as side effects of antipsychotics are dose dependent, and different to other antipsychotics, are related to the duration of treatment in patients using clozapine.[25-27] Consistent with this information, obsessive–compulsive symptoms were found to be more common in those receiving clozapine for a longer period of time in our study. Therefore, inquiring patients for OCD symptoms not only within the first few weeks of initiation but also later years of treatment is essential.

In a study examining 320 patients with TRS and schizoaffective disorder who were treated with clozapine between 1993 and 2007, more than half of the patients had at least one period of discontinuation, the most common reason for discontinuation was treatment non-compliance and side effects, and most of the side effects associated with withdrawal were hematological and central nervous system side effects.[14] In another study, in which 201 patients were followed for a 22-year treatment period, the most common reasons were drug or obligatory blood test incompatibility, neutropenia, and other side effects.[28] In a cohort study in which all patients (n=311) who started using clozapine for the 1st time between 2007 and 2011 were retrospectively investigated, 45% of the patients discontinued the treatment within the first 2 years, and a significant portion of this was in the first few months (20% in the first 3 months). Furthermore, Inada et al.[29] reported a clozapine discontinuation rate of 23.9% in a period of 1st year of treatment. It has been shown that the most important reason for discontinuation of treatment, both for clinicians and patients, is side effects (most frequently sedation, neutropenia, and tachycardia), and discontinuation due to side effects is more common, especially in the 1st month.[13] Clozapine treatment was terminated in one-fourth of the patients with schizophrenia and schizoaffective disorder included in our study. In addition, treatment of approximately one-third of patients whose clozapine treatment was discontinued in the first 6 months and half in the first year similar to results of studies in literature. Considering the reasons for discontinuation, irregular use and drug-related side effects constitute an important part, but there was no significant relationship between the time of discontinuation and reasons for this. To find possible predictors of the discontinuation of treatment, the reasons were collected under three groups as (1) the patient quitting the drug on his own as a result of irregular use, (2) intolerance to medical side effects, and (3) insufficient effect, and the factors that could cause this were investigated. According to the analysis, discontinuation is more frequent due to irregular use and insufficient effect in patients who have a higher number of suicide attempts. These groups may use irregularly or terminate the treatment since the expected effect of clozapine treatment cannot be achieved. These data also support the knowledge that the group whose clozapine treatment was discontinued due to unresponsiveness to clozapine consisted of patients with a worse prognosis from the beginning of the disease. There were no significant variables that could predict patients' discontinuation of treatment on their own or termination of treatment due to side effects.

African-American race, starting clozapine treatment at an advanced age, concomitant substance abuse, and no significant reduction in symptoms with clozapine have been re-

ported as general risk factors for discontinuing treatment.[14] In our study, there was no significant relationship between the duration of clozapine use, age, or history of concomitant alcohol and substance abuse when the patients under clozapine treatment were compared with those who discontinued it, but the rate of ECT, previously combined antipsychotic use, meeting the TSS criterion, and the total number of hospitalizations in patients who were discontinued with clozapine treatment, were found to be significantly higher. According to Kane's criteria, 40–70% of patients with schizophrenia defined as treatment resistant are also resistant to clozapine therapy and are referred to as clozapine resistant or highly resistant patients. In our study, approximately one-fourth of the group whose treatment was terminated due to insufficient effect. Therefore, with these data, it may be explained that the group whose treatment is terminated consists of schizophrenia patients with a worse prognosis than the patient group whose treatment is continuing and may be resistant to clozapine treatment.

There are some limitations of our study due to the cross-sectional and retrospective nature. First, results may not be representative of the general population and the side effects were not individually questioned because the data were based on patient files, and the significant part of the patients was followed in the general outpatient clinic. Furthermore, there was no control group consisting of patients using other antipsychotics, and some of the patients were using of other psychotropic drugs in addition to clozapine treatment. On the other hand, this study with a large participation on the reasons for discontinuation and side effects of clozapine which remains the gold standard in the treatment of psychosis may be beneficial in increasing treatment compliance.

Conclusion

In the light of these results, it is recommended that clinicians question common side effects and possible risk factors in each interview to ensure the continuity of treatment in patients using clozapine and try to keep the side effects under control with essential recommendations and interventions. It should be kept in mind that the patient group, which has a poor prognosis since the diagnosis of the disease, may not benefit from clozapine treatment, and if necessary, augmentation therapy should be considered.

Disclosures

Ethics Committee Approval: The study has been approved by the Ethics Committee of Istanbul Faculty of Medicine at its meeting numbered 16 on September 30, 2016 and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We also state that all participants gave their informed consent before their inclusion in the study.

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