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Reasons for clozapine discontinuation in patients with treatment-resistant schizophrenia

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A B S T R A C T

Although clozapine is more effective than other antipsychotics in the treatment of schizophrenia, the rate of its discontinuation is also high. The aim of this retrospective chart-review study was to investigate the causes of clozapine discontinuation in patients with treatment-resistant schizophrenia. This study included a total of 396 patients with schizophrenia, 240 still on clozapine therapy and 156 who discontinued clozapine, and compared their clinical characteristics. Those who discontinued clozapine had a longer history of illness and more hospitalizations before clozapine and tended to be older. Inadequate response was more common among clozapine discontinuers compared to continuers. The most common reason for discontinuation was the side-effects associated with clozapine (49%). Discontinuation from patient decision or by the psychiatrist due to noncompliance was the second (29.7%) and discontinuation due to lack of efficacy was the third most frequent reason (21.3%). The patients who discontinued clozapine because of cardiac side effects were younger, had shorter duration of clozapine use, and had lower maximum clozapine dose compared to the other discontinuers. Our findings point out the importance of enhancing psychiatrists' ability to handle manageable side effects to minimize discontinuations and maximize the benefits of clozapine in patients with treatment-resistant schizophrenia.

1. Introduction

Clozapine, a dibenzodiazepine developed in 1961, is an atypical antipsychotic with multiple receptor interactions exhibiting a unique efficacy profile for patients with treatment-resistant psychotic disorders. Approximately two-thirds of the patients who have not responded adequately to the first generation and other second generation antipsychotics seem to respond well to clozapine (Kane et al., 1988).

Discontinuation of antipsychotics is common in patients with schizophrenia (Lieberman et al., 2005). Rate of discontinuation is lower and time to discontinuation is longer for clozapine compared to other second-generation antipsychotics (Chan et al., 2016; Ndukwe and Nishtala, 2016; Kroken et al., 2014; Jung et al., 2011; Taylor et al., 2008; Haro et al., 2006). However, compliance to clozapine treatment is an important issue as the initiation of this medication is generally reserved for the treatment of resistant cases and alternative treatments initiated upon its discontinuation do not result in similar efficacy. Moreover, the reduced risk of suicide associated with clozapine treatment may reincrease upon its discontinuation (Patchan et al., 2015). The rates of discontinuation of clozapine treatment have been found to be in the range of 20 to 60% (Beex-Osterhius et al., 2018; Gee et al., 2018; Davis et al., 2014; Schneider et al., 2014; Pai and Vella, 2012; Moeller et al., 1995; Atkinson et al., 2007). One main factor influencing clozapine discontinuation is the wide range of side effects leading to serious challenges. Clozapine use is associated with various difficult-to-tolerate side effects including agranulocytosis and myocarditis which can be life-threatening. In a comprehensive review, Nielsen et al. (2013) suggest that agranulocytosis, myocarditis, cardiomyopathy, and a QTc interval >500 milliseconds should lead to prompt discontinuation of clozapine without rechallenge. Adverse reactions including ileus or subileus, neuroleptic malignant syndrome, venous thromboembolism, diabetic ketoacidosis and hyperosmolar coma are listed among the reasons for clozapine discontinuation with a potential risk for rechallenge. Other adverse reactions including neutropenia, leukocytosis, seizures, orthostatic hypotension, severe constipation, weight gain and metabolic abnormalities, moderately

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prolonged myocardial repolarization, eosinophilia, drug-induced fever, and sole tachycardia are reported to be manageable side effects which do not require clozapine discontinuation (Nielsen et al., 2013).

Risk factors for clozapine discontinuation, including side effects, have been investigated in several studies. Earlier studies have pointed out that older age and ethnicity increase the risk of clozapine discontinuation (Gee et al., 2018), but studies conducted in the last decade have not consistently replicated this finding. Some other risk factors were identified which necessitate further studies on the topic. Krivoy et al. (2011) conducted a retrospective analysis on 100 schizophrenia patients to compare the demographic and clinical characteristics of 58 patients continuing clozapine treatment to those of 42 patients who had discontinued it, in a mean follow-up period of 8 years. Twenty of the latter patients (47.6%) had discontinued clozapine due to non-adherence and 11 (26.2%) due to side effects. In this study, the predictors for clozapine discontinuation were older age at clozapine initiation and comorbid substance abuse. Davis et al. (2014) investigated the frequency and causes of clozapine discontinuations in 320 patients, which occurred over a 15-year period. More than half of the patients (57%) had at least one discontinuation. The two most common causes for discontinuation were non-adherence (35%) and side-effects (28%) with hematological side-effects accounting for 45% of these and central nervous system side-effects for 35%. Ethnicity, older age at initiation of clozapine, and unsatisfactory improvement in psychiatric symptoms were the main risk factors associated with discontinuation. Gee et al. (2018), however, recently reported that age, ethnicity, diagnosis and antipsychotic treatment history were not predictive of the risk of clozapine discontinuation. Among the 133 patients who were followed up for 4–9 years, 48 (36.1%) were found to discontinue clozapine at least once during the study period. Male patients were more likely (2.15 times higher) to stop taking clozapine. Similar to previous studies, the most common reason for discontinuation was patient refusal of the treatment. Legge et al. (2016) also investigated the risk factors, reasons and timing of clozapine discontinuation in a two-year retrospective cohort study of 316 patients with treatment-resistant schizophrenia. A total of 142 (45%) patients were found to discontinue clozapine and adverse drug reactions accounted for over half of such discontinuations, with sedation as the leading cause. Interestingly, high level of deprivation in the neighborhood where the patient lived was found to be associated with increased risk of discontinuation.

Clozapine discontinuation has also been investigated in schizophrenia patients at their earlier stages of illness. Shaker and Jones (2018) conducted a retrospective analysis on 25 patients with treatment-resistant schizophrenia under an early intervention service. The discontinuation did not produce significant effects on 1-year outcomes with respect to duration of inpatient or home treatment, total antipsychotic dose, number of alternative antipsychotics prescribed, number of hospital/home treatment episodes and number of adverse events. More than half (56%) of the patients remained clinically stable after discontinuation. As in previous studies, non-compliance was found to be the main reason (44%, $n = 11$) for discontinuation

In a recent investigation of clozapine discontinuation and rechallenge in Turkey at a university psychiatry clinic where clozapine was initiated algorithmically, a database search of 122 cases revealed 26 (21.3%) clozapine treatment discontinuations, including 9 (7,4%) rechallenges (Hun et al., 2017).

Some of the previous studies had different limitations from ours like small sample size (Shaker and Jones, 2018) and relatively short period of follow-up (Beex-Osterhuis et al., 2018). In this study, we aimed to further investigate the causes and risk factors leading to clozapine discontinuation in a large sample of patients with the inclusion of cases from multiple sites in Turkey. We hypothesized that there would be differences between those who discontinued clozapine and still use it in terms of clinical characteristics. We expected that discontinuations due to side effects or non-compliance would happen earlier in the course of treatment than discontinuations due to ineffectiveness.

2. Methods

In this retrospective chart review study, patients with treatment-resistant schizophrenia (TRS) who were prescribed clozapine were recruited from six sites in four cities in Turkey. From these sites, all the patients with TRS who discontinued clozapine and randomly selected clozapine users were included to compare their respective data. As Istanbul Faculty of Medicine's clozapine database covered the entire patients who either discontinued or still use it, we included all of them. We also included data on clozapine users from the other sites as long as they were able to send them before a predetermined deadline. Data were collected on demographic characteristics, duration of illness, type and number of antipsychotics used at adequate doses for at least six weeks before starting clozapine and antipsychotic polypharmacy.

Adequate and recommended maximum doses of antipsychotics, which are similar to those reported in international guidelines, were administered in accordance with the Psychiatric Association of Turkey's Treatment Guideline for Schizophrenia (Ucok and Soygur, 2010).

Clinical information gathered included patient's smoking status, daily consumption of cigarettes, history of alcohol/substance abuse, previous electroconvulsive therapies (ECT), number of hospitalizations, other antipsychotics, mood stabilizers or antiepileptic medications used with clozapine, and adverse effects of clozapine use. All patient files were screened manually and the reasons for clozapine discontinuation were obtained from descriptive case notes. If clozapine was discontinued because of a particular side effect, this was also recorded as a side effect leading to discontinuation. Although a formal checklist for side-effects was not utilized, the clozapine-related side-effects were recorded as noted by the patient and/or physician in patient file at routine outpatient visits.

Eighteen patients with a current or past history of clozapine use were excluded from the study because we were unable to obtain sufficient information about their disease and prior antipsychotic use from the charts. In patients who had more than one clozapine discontinuation, only the first one was recorded and evaluated. Clozapine was started in the six university hospitals for the patients who were aged 18–65 years and were admitted either as an inpatient or outpatient. All of the patients were Caucasians.

The study sample consisted of a total of 396 patients of whom 156 discontinued clozapine due to various reasons. The sample included 246 patients (66 discontinuers, 26.8%) from Istanbul Faculty of Medicine; 57 patients (26 discontinuers) from Kocaeli University Faculty of Medicine Department of Psychiatry, 27 patients from Ankara Faculty of Medicine (13 discontinuers), 27 patients from Ankara Atatürk Training Hospital (14 discontinuers), 22 patients from Hacettepe Faculty of Medicine (22 discontinuers), and 16 patients from Celal Bayar University Faculty of Medicine (15 discontinuers). Clozapine was discontinued either by the patients' own decision or by the treating physician. We compared the clinical data of clozapine discontinuers with those of 240 patients with schizophrenia who still used clozapine. The study was approved by the Institutional Review Board of Istanbul Faculty of Medicine.

2.1. Definitions

Treatment-resistant schizophrenia (TRS) was defined as no response to treatment with at least two antipsychotics at appropriate doses used for at least six weeks. This definition is very similar to the recently published TRS criteria (Howes et al., 2017). Scales for change in symptom severity (if any scale was used) and/or scales measuring the extent of symptom severity and the opinions of the physician, patient or relatives were used for the identification of TRS. Based on these, patients were classified in three categories; patients giving no/minimal response to clozapine, those giving moderate response and those giving

remarkable response. A prerequisite for an accurate classification was clozapine use for at least one month after reaching the target dose. As detection of clozapine levels is not used in routine practice, the minimum target dose of 300 mg/day was used as stated in the Psychiatric Association of Turkey's Treatment Guideline for Schizophrenia (Ucok and Soygur, 2010).

Response to treatment was assessed by global use of all the above-mentioned resources.

The lapse between fulfilling the TRS criteria and the first clozapine use in treatment-resistant patients was expressed as the time passed from the end of the second adequate antipsychotic treatment episode to the first clozapine use as previously described by Howes et al. (2012). The time between week 6 of this trial and the first use of clozapine was used in patients who were nonresponsive to a second antipsychotic drug despite adequate dose and duration.

2.2. Statistical analyses

Kolmogorov-Smirnov test was used to see if the variables were normally distributed. We used t-tests for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Chi-square test for categorical variables. To compare the three groups of discontinuers, we used Kruskal-Wallis test. A post hoc analysis was made using Mann-Whitney U test. The threshold for significance for *p*-value was 0.05. Statistical analyses were conducted using SPSS software version 16.0.

3. Results

The socio-demographic and clinical characteristics of the patients are presented in Table 1.

All the patients from Istanbul Medical Faculty (n = 246) who have used clozapine between 2000 and 2017 were included in the study. Thus, a clozapine discontinuation rate of 26.8% was calculated based on the data from this center.

Although time to discontinuation was as long as 216 months in some clozapine discontinuers, 34.5% of the discontinuations happened in the first 6 months and 48% in the first 12 months. The mean time to discontinuation was 34.3 months and median 14.4 months.

3.1. Clinical data differences between the patients who discontinued clozapine and who still use it

We found that those who discontinued clozapine had longer duration of illness and tended to be older compared to the patients who were still on clozapine treatment. No/minimal response to clozapine according to the treating psychiatrist was more common among clozapine discontinuers. Use of a combination of clozapine with an antiepileptic or antidepressant was less frequent in the discontinuer group. There was no significant difference between the two groups in terms of education, sex, working status, smoking, history of ECT, number of past antipsychotic trials with adequate dose and duration before clozapine, or time to start of clozapine after meeting TRS criteria (Table 1).

3.2. Reasons for clozapine discontinuation and related clinical characteristics

The most common reason for discontinuation was side effects associated with clozapine use (n = 77, 49%). Discontinuation from patient decision or by the psychiatrist due to noncompliance was the second (n = 46, 29.7%) and discontinuation by the psychiatrist due to lack of efficacy was the third most frequent reason (n = 33, 21.3%).

Leukopenia, sedation, and seizure/myoclonic jerks were the three most common causes for discontinuation. Hypersalivation, incontinence, tachycardia, myocarditis, obsessive-compulsive symptoms, weight gain, diabetes mellitus and orthostatic hypotension were the other side effects leading to clozapine discontinuation (Table 2).

First, we compared the clinical characteristics of the patients who discontinued clozapine because of side effects, noncompliance or lack of efficacy. Clinical characteristics of these three groups are presented in Table 2. A significant difference was found in the maximum clozapine dose used by the three groups (χ^2 = 9.76, df = 2, p = 0.008). A post hoc analysis showed that the maximum dose of clozapine was lower in those who discontinued clozapine due to side effects (347.2 ± 247.9) than in those who discontinued it due to noncompliance (440 ± 200.4 mg/day, p = 0.024) and those who discontinued it due to lack of efficacy (467 ± 245.4 mg/day, p = 0.008). Similarly, the final clozapine dose differed significantly among the three groups (χ^2 = 8.77, df = 2, p = 0.01). We found in the post hoc analysis that clozapine dose was lower in the side effect group than in the noncompliance group (207.5 ± 146.6 vs 346.1 ± 183.2 mg/day Z = 2.91, p = 0.004). However, there were no differences among those who discontinued

Table 1
Clinical and sociodemographic characteristics of patients on clozapine treatment.

	Total (n = 396)	Clozapine Discontinuers (n = 156)	Clozapine Continuers (n = 240)	χ^2, t, Z	p
Age (years, mean ± SD)	38,2 ± 11,5	39,5 ± 11,8	37,3 ± 11,3	t = 1,86, df = 392	0,06
Education (years)	10,9 ± 3,5	11,5 ± 3,3	10,6 ± 3,6	t = 1,8, df = 390	0,07
Sex (Male)	64,9%	66,1%	64,7%	X^2 = 20,76 df = 1	n.s.
Marital status (Single)	80,3%	80,5%	74,8%	χ^2 = 1,2, df = 2	n.s
Occupation (None/nonfunctional housewife)	79,2%	78,8%	80,3%	χ^2 = 0,87, df = 3	n.s.
Duration of illness (years)	16,1 ± 10,8	17,6 ± 13,5	15,1 ± 8,5	Z = 2,28,	0,02
Duration between onset of illness and to start clozapine (months)	110,4 ± 90,6	107,7 ± 96	111,5 ± 86,9	Z = 1,04	n.s.
Duration of clozapine treatment (months)	54 ± 56,3	34,3 ± 41,9	66,9 ± 60,7	Z = 6,28	<0,001
Maximum dose of clozapine (mg/day)	423,5 ± 189,8	439,3 ± 166,8	400,1 ± 219,2	Z = 2,48	0,01
Last clozapine dose (mg/day)	341,3 ± 172,2	263,6 ± 183,3	371,4 ± 158,7	Z = 4,98	<0,001
No/minimal response to clozapine according to treating psychiatrist	27,9%	29,5%	16,4%	χ^2 = 16,9, df = 3	<0,001
Number of previous hospitalizations before clozapine	3,1 ± 2,2	2,3 ± 2,7	3,8 ± 3,6	Z = 3,01	0,002
Number of antipsychotics before clozapine	2,53 ± 1,31	2,77 ± 1,51	1,44 ± 1,57	Z = 1,44	n.s.
Duration between time to meet TRS criteria and start of clozapine (months)	27,1 ± 30,5	22,9 ± 29,4	27,6 ± 29,5	Z = 1,14	n.s.
Past ECT before clozapine treatment	27,6%	32,3%	24,3	χ^2 = 3,53, df = 1	n.s.
Antidepressant combined with clozapine	39,2%	35,9%	41,4%	χ^2 = 5,67, df = 1	0,05
Antiepileptics combined with clozapine	15,7%	12,8%	17,6%	χ^2 = 3,11	0,01
Other antipsychotics combined with clozapine	58,5%	57,1%	59,4%	χ^2 = 1,52, df = 1	n.s.

Table 2
Clinical and sociodemographic characteristics of the patients who discontinued clozapine.

	Discontinuation due to side effects (n = 396)	Discontinuation due to noncompliance (n = 156)	Discontinuation due to lack of effectiveness (n = 240)	P
Age (years, mean ± SD)	40,2 ± 13,5	38,5 ± 10,9	38,5 ± 9,5	n.s.
Education (years)	12 ± 3,3	10,4 ± 3,3	12,1 ± 3,3	n.s
Sex (Male)	66,7%	63%	66,7%	n.s.
Duration of illness (years)	18,7 ± 17,7	16,5 ± 8,7	16,8 ± 6,3	n.s
Duration between onset of illness and to start clozapine (months)	111,2,4 ± 103,6	111,2 ± 95,5	92,4 ± 75	n.s.
Duration of clozapine treatment (months)	29,7 ± 39,7	40,1 ± 49,8	35,8 ± 36,8	n.s
Maximum dose of clozapine (mg/day)	346,5 ± 209,3	440 ± 200,7	467,4 ± 245,1	n.s
Last clozapine dose (mg/day)	207,5 ± 146,6	346,8 ± 183,3	302,9 ± 146	n.s.
Number of antipsychotics before clozapine	2,6 ± 1,5	2,8 ± 1,4	2,8 ± 1,7	n.s.
Duration between time to meet TRS criteria and start of clozapine (months)	19,1 ± 30	19,2 ± 20,9	37 ± 42,1	n.s.
Past ECT before clozapine treatment	26,7%	39,1%	36,4	n.s.
Antidepressant combined with clozapine	32%	23,9%	60,6%	0,05
Antiepileptics combined with clozapine	10,7%	15,2%	15,2%	0,01
Other antipsychotics combined with clozapine	52%	56,5%	69,1%	n.s.

clozapine due to side effects and other reasons with respect to age, sex, duration of illness, or clozapine use, or psychotropic combinations.

Concomitant use of mood stabilizers and antidepressants was more frequent ($\chi^2 = 12.2$, $df = 2$, $p = 0.002$) in the lack-of-efficacy group (60.6%) compared to the noncompliance (24.9%) and side effect groups (36.6%).

We also compared each individual group of patients who discontinued clozapine due to one of the above-mentioned reasons to the other discontinuers (i.e. to the patients who belong to the other two groups). The noncompliance group had higher smoking rates (53.8% vs 46.2%, $\chi^2 = 6.61$, $df = 1$, $p = 0.03$) compared to the other discontinuers. There was more use of clozapine in combination with other antipsychotics (71.9% vs 49.1%, $\chi^2 = 18.5$, $df = 1$, $p = 0.029$) or mood stabilizers (62.5% vs 32.2%, $\chi^2 = 13.8$ $p = 0.03$) in patients who discontinued due to ineffectiveness as compared to the other two groups.

A comparison of the patients who had the illness for ≤5 years (n = 14) and those who had it for >5 years (n = 142) with respect to the reason for discontinuation (own decision, ineffectiveness or side-effects) showed no significant difference between these two groups.

3.3. Clinical characteristics related to frequent side-effects which cause clozapine discontinuation

The clinical and socio-demographic characteristics related to the most frequent side-effects (namely leukopenia, sedation, cardiac side-effects, and seizure/myoclonic jerks) which caused discontinuation of clozapine were also evaluated. Those who discontinued clozapine due to seizures were older than rest of the clozapine discontinuers (n = 15, 49.1 ± 15.8 vs 38.6 ± 10.9 years, $t = 3.24$, $df = 154$, $p = 0.001$). The maximum clozapine dose was lower in patients who discontinued clozapine due to sedation (n = 14, 283.3 ± 180.3 mg/day vs 410.9 ± 220.2 mg/day, $Z = 1.89$, $p = 0.05$). Duration of clozapine treatment was longer in patients who discontinued clozapine due to leukopenia (n = 15, 74.8 ± 50.1 vs 31.4 ± 40.7 months, $Z = 3.03$, $p = 0.002$). The patients who discontinued clozapine because of cardiac side effects (orthostatic hypotension, tachycardia and myocarditis, n = 12) were younger (33 ± 8.6 vs 40 ± 11.8, $Z = 1.91$, $p = 0.05$), had shorter duration of clozapine use (1.04 ± 0.35 vs 36.7 ± 42.62 months, $Z = 4.86$, $p < 0.001$) and had a lower maximum clozapine dose (177.2 ± 86.9 vs 416.6 ± 188.4 mg/day, $Z = 3.71$, $p < 0.001$) compared to the other discontinuers.

3.4. Common clozapine-related side-effects in the whole group of patients

Sedation was the most frequent clozapine-related side effect as noted in the files of the patients who discontinued clozapine. It was followed by weight gain, hypersalivation, increase in new onset of obsessive-compulsive symptoms, orthostatic hypotension, incontinence, seizure/myoclonic jerks, leukopenia, constipation and sexual side effects, and myocarditis (Tables 2 and 3).

4. Discussion

In this retrospective chart review, we analyzed reasons for clozapine discontinuation and the clinical characteristics related to such

Table 3
Clozapine related side effects in whole patient group, and among clozapine discontinuers.

Clozapine-related side effects	Among the reasons of discontinuation due to side effects n = 76	%	Time to Discontinuation (months)	In all sample n = 396	%
Leukopenia	15	19,7	21 ± 36,2	18	4,6
Sedation	12	15,7	29,7 ± 35,2	165	41,4
Seizure/myoclonic jerks	10	13,1	74,8 ± 50,1	17	4,3
Hypersalivation	7	9,2	9,4 ± 6,9	112	28,1
Incontinence	6	7,8	27,8 ± 18,8	44	11
Tachycardia	6	7,8	1,1 ± 0,9		
Myocarditis	4	5,2	1 ± 0,1	5	1,24
Obsessive-compulsive symptoms	4	5,2	55,5 ± 46,8	49	12,3
Weight gain	3	3,9	31,5 ± 11,4	116	29,1
Diabetes mellitus and other metabolic disorders	2	2,7	6,1 ± 1,5		
Orthostatic hypotension	2	2,7	1 ± 0	36	9,1
Other reasons	5	6,5			
Sexual side effects	–	–		10	2,5

discontinuation. Our hypothesis was partially confirmed. Those who discontinued clozapine had a longer history of illness, more past hospitalizations, and limited benefit from clozapine treatment. However, we did not find any differences between clozapine discontinuers and those who continued clozapine treatment with respect to a large number of other clinical characteristics.

We did not limit ourselves with a time frame like one or two years, but aimed to include patients who used clozapine for longer periods. Our clozapine discontinuation rate of 26.8%, which is based on a single site data ($n = 246$), is similar to the findings of Inada et al. (2018) who reported a clozapine discontinuation rate of 23.9% in a period of six and a half years. On the other hand, Legga et al. (2016) reported a discontinuation rate of 45% within 2 years after starting clozapine. Similarly, Forrester et al. (2015) reported that 27% of the people who commenced clozapine stopped it before week 18 and 52% within the first three weeks. They also reported that, once the patients reached the maintenance, time to cessation prolonged up to 93 months. It seems that discontinuations happen more in early periods of starting clozapine, tending to decrease later.

We found that more than one third of the discontinuations were recorded in the first six months and almost half of them in the first year of clozapine treatment. Our rates of early discontinuation were similar to those reported by Pai and Vella (2012) who also stated that half of the discontinuations were in the first six months. These findings suggest that close monitoring of compliance and side effects in the months right after clozapine initiation is important in minimizing early discontinuations. Our findings as to how certain clinical characteristics related to specific side effects also offer some clues regarding their monitoring. We found that cardiac side effects that caused discontinuation of clozapine occurred in the first month of treatment in younger patients. Therefore, if clinicians pay special attention to manageable cardiac side effects like tachycardia and orthostatic hypotension in the first month of treatment, particularly in younger patients, it will be possible to take measures to treat them. On the other hand, seizures or myoclonic jerks that lead to discontinuation will occur more likely in patients who are in their forties or older. As there is a dose-response relationship between daily dose and risk of seizures (Grover et al., 2015; Caetano, 2014), clinicians should be more cautious when escalating the clozapine dose to its maximum therapeutic limit.

It was not surprising that the number of patients with minimal response to clozapine was higher in the discontinuation group . However, lack of response to clozapine is only the third top reason for discontinuation. It has been reported that approximately 40% of the patients who have used clozapine had limited benefit from this treatment (Siskind et al., 2017). Discontinuation of clozapine has been recommended in case of nonresponse after a reasonable time to reach a conclusion because of its metabolic and other potential side effects (Siskind et al., 2016). Our findings suggest that psychiatrists tend to continue clozapine treatment even in case of nonresponse, until a disturbing side effect appears.

Unlike previous studies reporting noncompliance as the most common reason for discontinuation (Shaker and Jones, 2018; Mustafa et al., 2015; Davis et al., 2014), we found that clozapine-related side effects were responsible in majority of the patients in our sample. This may be due the difficulties clinicians faced in handling the side effects of clozapine. Also, one can speculate that patients who are reluctant to continue clozapine treatment use side effects as a justification for their noncompliance.

Contrary to previous reports (Gee et al., 2018), refusal of regular blood count was not recorded in our case as a reason for discontinuation. This may be because the psychiatrists explained the procedure in advance and did not start clozapine if the patient refused to collaborate. Another possibility is that the patients who did not want to give blood samples anymore might have stopped clozapine without informing their psychiatrist of the reason.

We found that discontinuation due to leukopenia happened also in the later phases of the treatment. This indicates the importance of continuous blood count monitoring beyond the early phases of the clozapine treatment.

As we recently reported a negative relationship between delayed onset of clozapine treatment and the benefit that can be derived from it (Ucok et al., 2015), we expected to find that the lapse between meeting TRS criteria and start of clozapine would be longer in those who discontinued clozapine due to nonresponse. Similarly, we expected to find that discontinuation due to nonresponse would be lower in patients with shorter duration (<5years) of illness. However, this was not the case; clozapine-related side effects turned out to be the most common reason for discontinuation rather than lack of response. This may explain our above-mentioned findings.

Our findings suggest that clinicians tried to avoid discontinuation of clozapine by reducing its daily dose in case of side effects or combining clozapine with other antipsychotics or mood stabilizers in case of inadequate response. Similarly, contrary to the reports of high prevalence of some side effects like sedation, we found that such side effects rarely caused discontinuation; clozapine was discontinued due to some manageable side effects (Nielsen et al., 2013) like leukopenia, seizures, tachycardia, or weight gain. We observed that some psychiatrists decided to stop clozapine in patients who had mild leukopenia but no agranulocytosis. It seems that even psychiatrists who work in a university hospital can be reluctant to continue clozapine and, at the same time, manage the adversities when it comes to hematological side effects.

Our study has some limitations. First of all, because of the retrospective nature of the study, the accuracy of our findings relied on the quality of the records in patient files. Second, although the best was done to be precise, it was difficult in some cases to differentiate whether the reason for discontinuation was just due to the patient's noncompliance or the side effects. As all the patients in this study were treated in university hospitals, our findings may not reflect the general situation in Turkey, so the generalizability of our findings is limited. Another factor limiting the generalizability of our findings was that the patients who still used clozapine in our sample represented only a subgroup of all clozapine users in the study sites. Nonetheless, our study also had some strong points; it included a control group to compare clozapine discontinuers to patients who still use clozapine in a diagnostically homogenous sample and a large number of patients were evaluated in a long period of time.

In summary, we have found that discontinuation of clozapine treatment is common in Turkey and the side effects related to its use is the most common reason leading to clozapine discontinuation. Our findings point out the importance of enhancing psychiatrists' ability to handle manageable side effects in order to minimize discontinuations and maximize the benefits of clozapine in patients with treatment-resistant schizophrenia.

As a next step, we are planning to study the clinical course of patients after clozapine discontinuation and the predictors of rechallenge of clozapine in a larger group of patients with schizophrenia.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.01.110.

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