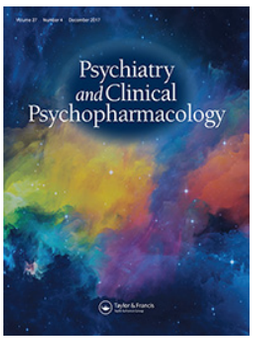

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Prescribing trends in treatment-resistant schizophrenia

Aynur Görmez[a], Ayşe Kurtulmuş[b], Can Tuncer[a] and Serhat Çıtak [a]

[a]Department of Psychiatry, Istanbul Medeniyet University, Istanbul, Turkey; [b]Department of Psychiatry, Bezmialem Vakif University, Istanbul, Turkey

ABSTRACT

Objectives: Schizophrenia is a common mental health condition associated with significant morbidity and excess early mortality. Treatment-resistant schizophrenia (TRS) occurs in about one in three patients diagnosed with schizophrenia. The aim of this study was to identify attitudes of a nationally representative sample of psychiatrists towards pharmacotherapy of patients with TRS, the potential factors related to their choice of various regimens, and to investigate the clinical outcomes of different methods employed.

Methods: Psychiatrists were contacted through national e-groups and various psychiatry conventions. They provided information about their professional and demographic characteristics. They were asked to describe clinical and demographic characteristics of an adult patient with TRS under their care for at least 3 months. They reported on the medication change they made and the effect of this intervention on the positive symptoms and functioning of the patient.

Results: Among the 207 patients reported on, only 28.7% were on monotherapy for TRS immediately before the change in medication. With the change made in treatment regime, 40.1% were switched to a different antipsychotic agent as monotherapy, 40.6% received combination therapy with two or more antipsychotic agents, 1.4% received high-dose antipsychotics, and 4.8% had augmentation with antidepressants or mood stabilizers. 13.1% psychiatrists employed more than one method. Of the whole sample, 48.3% were put on clozapine either as monotherapy or with other medications. The monotherapy and combination groups were compared in terms of characteristics of patients and prescribers, which revealed no significant difference ($p > .05$). There was also no difference found on the outcome variables of two groups ($p > .05$).

Conclusions: Although polypharmacy was found to be a common practice, there seemed to be a comparably good ratio of clozapine utilization and of attempts of switching to monotherapy among the prescribers. There were no significant patient- or prescriber-related factors in relation to preference of treatment regimens, which need further investigation on larger samples.

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Schizophrenia; treatment resistance; antipsychotics; polypharmacy; clozapine

Introduction

Schizophrenia is a common mental health condition and is associated with significant morbidity and excess early mortality [1]. Antipsychotics are still the mainstay of treatment of schizophrenia. Despite the increase in the number of available antipsychotics, treatment of schizophrenia continues to pose a challenge to clinicians. It is estimated that approximately one-third of patients with schizophrenia experience persistent psychotic symptoms despite adequate treatment with antipsychotics [2]. Treatment-resistant schizophrenia (TRS) puts a significant burden on patients' well-being. A recent review found decreased quality of life, increased medical costs, and increased rates of serious comorbidities compared with patients with schizophrenia in general [3].

There is no unified definition of treatment resistance in schizophrenia. Most international guidelines require the failure of at least two different antipsychotic trials (some requires one to be second generation) at a therapeutic dose over a period of 2–8 weeks before describing treatment resistance [4,5]. The definition of treatment resistance evolved over time from exclusively focusing on positive symptoms to incorporating negative and various kinds of disability symptoms [6,7]. However, positive symptoms remain a central focus as the main target of antipsychotics and the primary outcome in the early clozapine trials, which defined treatment resistance [8].

Different approaches are taken by clinicians when they encounter a patient with TRS. The options include switching to another antipsychotic including clozapine, high-dose prescribing, adding another antipsychotic or adjunct medication or sometimes trying more than one of these at the same time.

High-dose prescribing is treatment with an antipsychotic above a recommended maximum dose.

CONTACT Aynur Görmez aynurdemirel@yahoo.com

Although some patients may benefit from this approach, there is no evidence that high doses of antipsychotics have any advantages over standard doses, in fact high doses are associated with a greater side effect burden and none of the international treatment guidelines support this option for TRS [9].

Switching from one antipsychotic to another one (as a monotherapy) is a common practice when one failed to improve the symptoms. There is some evidence to suggest that olanzapine, risperidone, and amisulpride might be superior to other second-generation antipsychotics [10,11].

Simultaneous use of two drugs of the same group is called combination treatment. There are concerns about side effect burden and lack of robust evidence for benefit of use of antipsychotic combinations [12].

Co-administration of two drugs of different classes is defined as augmentation, for example adding antidepressant or mood stabilizer to an antipsychotic in order to enhance the efficacy of the antipsychotic. There is inadequate evidence of benefit of augmentation strategies in TRS cases other than targeting specific symptoms [13].

Although there are studies conducted in Turkey on the use of polypharmacy and/or excessive dosing in the treatment of schizophrenia [14–17], to our knowledge, there is no previous national study looking into prescribers' attitudes towards pharmacological management of patients with TRS. The aim of this study was to identify attitudes of a nationally representative sample of psychiatrists towards pharmacotherapy of patients with TRS, the potential factors related to their choice of various regimens, and to investigate the clinical outcomes of different methods employed.

Material and methods

Participants and procedures

A nationally representative sample of psychiatrists was invited to take part in the survey between November 2016 and May 2017. First-year psychiatry trainees were excluded.

According to information provided by the Turkish Psychiatric Association (TPA), there are around 3800 psychiatrists registered with the TPA, as of 2017. The psychiatrists were contacted through e-groups of Turkish psychiatrists for online version of the survey instrument and through various national and international psychiatry congresses for the paper version. Ethical approval for the study was granted by the ethical committee of the Bezmialem Vakıf University.

The criteria for included cases were described as follows: the patient previously had been on at least two different antipsychotics each for at least 6 weeks and continued to have symptoms in the form of delusions and/or hallucinations/ disorganized speech/behaviour and therefore was judged to be treatment resistant by the psychiatrist. The patient had been under the care of the prescriber for at least 3 months in the last one year.

Survey instrument

The questionnaire was subdivided into two sections: A about the prescriber and B about the patient covering the following four main areas: (1) Demographic and professional characteristics of the psychiatrists, (2) Demographic and clinical characteristics of the patients, (3) Type of medication change and (4) Effectiveness of the change.

In Section A, information was collected on demographic and professional characteristics of the psychiatrists including age, gender, years in clinical practice, main setting of work, professional position, caseload of patients with schizophrenia, monthly number of hours spent for professional development, weekly number of meetings with pharmaceutical representatives, and the number of pharmaceutical industry-sponsored education programmes attended in the previous year. In addition, on a Likert scale from 0 to 5, they were asked to rate their familiarity with various clinical practice guidelines for the treatment of schizophrenia, such as American Psychiatric Association (APA), National Institute for Clinical Excellence (NICE)/British Association of Psychopharmacology (BAP), Canadian Psychiatric Association (CPA), and TPA Guidelines.

In Section B, psychiatrists were asked to provide information about the clinical and socio-demographic characteristics of the patients including age, gender, marital and employment status, lifetime co-occurring psychiatric conditions including suicide attempts and previous psychiatric admissions. Each psychiatrist was asked to report about only one of their TRS cases. We asked them provide information about (1) the patient's lifetime treatment history, (2) the medications they were on immediately before the current intervention, and (3) the current pharmacological intervention that psychiatrists participated in the present survey reported to have made. The type of medication change was asked to be categorized into the following four groups: switching (monotherapy), combination, high-dose prescribing, or augmentation. They also provided their overall impression of effectiveness of the change in controlling psychotic symptoms on a Likert response scale ranged from 1 to 5, with higher scores indicating greater effectiveness. In addition, psychiatrists also provided Global Assessment of Functioning (GAF) scores both immediately before and after the medication change.

Data analyses

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 20.0 [18]. In addition

to descriptive statistics, the associations between patient- and prescriber-related factors and the preferred type of change in treatment regimen were analysed by using chi-square analyses for categorical variables and Student's *t*-test for continuous variables. Patients whose treatments were switched to another antipsychotic or for whom two or more antipsychotics were co-prescribed were compared. Analysis of covariance was conducted to compare the effectiveness of the two different interventions on GAF scores. The independent variable was the type of change and the dependent variable was GAF score after the treatment change. Pre-change GAF scores were used as the covariate in this analysis. All analyses were two-sided with alpha set at 0.05.

Results

Prescribers

A total of 244 psychiatrists responded to the survey. One of the respondents was a first-year psychiatric trainee who was excluded from the study. Of the remaining 243 respondents, 29 did not fill out the Section B. Among the remaining 214 respondents, 7 did not specify the medication change made. Two hundred and seven respondents who filled in the both sections and stated the type of change in treatment were included in the analysis.

The mean age of psychiatrists was 36.25 ± 9.32 years and 55.1% were female. Majority of psychiatrists (65.2%) practiced in a general/university hospital, 46.4% mainly worked at outpatient setting, 11.1% at inpatients, and 42.5% worked equally at both settings. Among 206 practitioners, who indicated their professional position, 16 (7.8%) were professors, 7 (3.4%) were associate professor, 16 (7.8%) were assistant professors, 95 (46.1%) were specialist psychiatrists, and 72 (35.0%) were psychiatric trainees. The mean duration of psychiatric practice of the participants was 8.99 ± 8.46 years. The average number of patients with schizophrenia seen in a week was 21. They also reported spending 25.57 ± 24.83 hours/month on average for reading for professional development, being visited by pharmaceutical representatives 6.03 ± 4.68 times a week and attending 2.89 ± 3.54 pharmaceutical industry-sponsored educational programmes in the previous year. Concerning familiarity with guidelines for schizophrenia, they gave the highest ratings for TPA guidelines (mean score was 3.3, on a 0–5 point Likert scale, SD: 1.3), followed by APA (mean: 2.7, SD: 1.4), NICE/BAP (mean: 2.1, SD: 1.5), and CPA (mean: 1.9, SD: 1.6).

Patients

The mean age of patients was 36.6 ± 10.1 years and the 62.3% of patients were male. The majority of patients had never been married (64.6%) and currently unemployed (87.9%). Patients had been under the care of their current psychiatrist approximately for 20 months. 72.1% of patients had a history of lifetime psychiatric comorbidity; 35.5% were diagnosed with a major depressive episode, 22.0% with an anxiety disorder, 15.5% with obsessive compulsive disorder, and 16.5% with a substance use disorder. Eighty-five per cent of the patients had a history of admission to an inpatient psychiatry unit, and past suicide attempt was reported by 22%.

Regarding patient's lifetime treatment history, 98% of them had a history of treatment with any of the non-clozapine second-generation antipsychotics, 80.9% with first-generation antipsychotics, 18.7% with clozapine, 9.5% with a mood stabilizer, and 18.8% with an antidepressant. Regarding the medications they were on immediately before the reported change in their treatment, this information was not provided for nine patients. However, of the remaining 198 patients, 122 (61.6%) were already on combination treatment with two different antipsychotics and 57 (28.7%) were on monotherapy with a single antipsychotic agent and 19 (0.95%) patients were on augmentation with a different class of psychotropic drug added to an antipsychotic agent.

Choice of treatment and related factors

With respect to the current medication change the psychiatrists reported to have made; of the 207 patients in the sample, 84 patients (40.6%) received combination therapy with two or more antipsychotic agents, 83 patients (40.1%) were switched to a different antipsychotic agent as monotherapy, 3 patients (1.4%) received high-dose antipsychotics exceeding recommended maximum dose, and 10 patients (4.8%) had augmentation with antidepressants or mood stabilizers. For 27 patients (13.1%), psychiatrists reported to have chosen two different methods at the same time. However, the analysis here focused on switch (monotherapy) and combination groups in order to avoid confounding factors such as comorbid disorders and also because of the small sample size of other groups (Table 1).

In the switch (monotherapy) group, 50 patients (60.2%) were switched to clozapine, 20 (24.1%)

Table 1 . Type of intervention.

Medication change made to address treatment resistance (*N*:207)	*N*	%
Monotherapy (switching to a different antipsychotic)	83	40.1
Combination therapy with two or more antipsychotics	84	40.6
Augmentation therapy	10	4.8
High-dose antipsychotic	3	1.4
Two different methods	27	13.1
Clozapine treatment[a]	100	48.3

[a]As a monotherapy or part of any of the interventions above.

Table 2. Characteristics of psychiatrists who managed patients with treatment-resistant schizophrenia by either monotherapy or combination treatment.

	Monotherapy (*N*: 83)			Combination (*N*: 84)					
Psychiatrist' characteristics	Total N	*N*	%	Total *N*	*N*	%	Test statistics	df	*p*
Demographic and practice characteristics									
Age (M ± SD)	36.04 ± 9.86			36.17 ± 8.61			$t = -0.09$	162	.93
Gender (Female)	83	47	56.6	84	45	53.6	$X^2 = 0.16$	1	.81
Years in clinical practice	9.57 ± 9.08			8.28 ± 7.54			$t = 0.99$	161	.70
Professional position									
Academic	82	17	20.7	84	13	15.5	$X^2 = 0.77$	1	.50
Non-academic		65	79.3		71	84.5			
Main setting of work:									
Inpatient	83	10	12	84	6	7.1			
Outpatient		41	49.4		46	54.8	$X^2 = 1.28$	2	.53
Both inpatient and outpatient		32	38.6		32	38.1			
Case load of patients with schizophrenia (M ± SD)	21.52 ± 24.07			17.78 ± 17.11			$t = 1.15$	162	.25
Monthly number of hours spent for professional development(M ± SD)	26.76 ± 26.09			21.08 ± 16.33			$t = 1.67$	135.5	.10
Weekly number of meetings with pharmaceutical representatives (M ± SD)	5.73 ± 4.04			6.62 ± 5.35			$t = -1.19$	161	.23
Number of pharmaceutical industry-sponsored education programmes attended in the previous year (M ± SD)	2.96 ± 4.09			2.88 ± 2.83			t = 0.15	160	.88
Familiarity with practice guidelines (M ± SD)									
TPD	3.30 ± 1.37			3.22 ± 1.12			$t = 0.42$	152.2	.67
APA	2.63 ± 1.44			2.68 ± 1.20			$t = -0.24$	153.1	.81
NICE/BAP	2.12 ± 1.56			2.27 ± 1.36			$t = -0.63$	149	.53
CPA	1.83 ± 1.53			1.84 ± 1.54			$t = -0.04$	152	.97

switched to a non-clozapine second-generation antipsychotic, and only 1 switched (1.2%) to a first-generation agent. For the remaining 12 (14.4%) patients, the post-switch antipsychotic was not specified. Among the 20 patients who were switched to a non-clozapine second-generation antipsychotic, 8 (9.6%) were commenced on long-acting antipsychotics.

In the combination group, 38 patients (45.2%) were put on clozapine along with a different antipsychotic and 36 (42.9%) were on combination therapy with non-clozapine antipsychotics. For the remaining 10 (11.9%), there were no details of the combination. Of the total 207 patients, 33 (15.9%) were on clozapine immediately before the change, 2 of them were switched to another antipsychotic as monotherapy, 19 had another antipsychotic added, 1 had dose escalation, 4 had augmentation therapy and 7 had both augmentation and combination with another antipsychotic. Overall, a total of 100 patients (48.3% of the whole sample) were reported to be on clozapine either as monotherapy or with other psychotropics.

As shown in Table 2, there was no significant difference between two treatment (switch vs. combination) preferences regarding psychiatrists' age, gender, years in clinical practice, professional position, primary treatment setting, caseload of patients with schizophrenia, monthly number of hours spent for professional development, weekly number of meetings with pharmaceutical representatives, and the number of pharmaceutical industry-sponsored education programmes attended in the previous year.

The results for two treatment groups on positive symptoms and functioning of patients, with respect to patients' demographics and clinical characteristics, were shown in Table 3. No significant differences were seen between treatment groups regarding patients' age, gender, marital status, employment status, comorbid psychiatric conditions, duration of

Table 3. Socio-demographic and clinical characteristics of patients whose treatment-resistant schizophrenia was managed by monotherapy or combination treatment.

	Switch (*N*:8 3)			Combination (*N*:8 4)					
Patient' characteristics	Total *N*	*N*	%	Total *N*	*N*	%	Test Statistic	df	*p*
Demographics									
Age (M ± SD)	35.28 ± 9.64			37.23 ± 9.94			$t = -1.27$	161	.21
Gender (Female)	83	32	38.6	84	31	36.9	$X^2 = 0.05$	1	.95
Marital Status (Never married)	82	57	69.5	84	52	61.9	$X^2 = 1.07$	1	.39
Employment Status (Not employed)	83	71	85.5	84	76	90.5	$X^2 = 0.96$	1	.46
Clinical characteristics									
Lifetime psychiatric comorbidity	78	53	67.9	81	57	70.4	$X^2 = 0.11$	1	.87
Major depression	80	24	30.0	82	31	37.8	$X^2 = 1.10$	1	.38
Anxiety disorder	80	15	18.8	82	18	22.0	$X^2 = 0.26$	1	.76
Obsessive Compulsive disorder	80	10	12.5	82	11	13.4	$X^2 = 0.03$	1	.86
Substance Use Disorder	80	14	17.5	82	10	12.2	$X^2 = 0.90$	1	.47
Suicide attempt	82	13	15.9	84	18	21.4	$X^2 = 0.85$	1	.47
Psychiatric hospitalization	83	74	89.2	84	67	79.8	$X^2 = 2.80$	1	.14
Duration of treatment with the psychiatrist (month) (M ± SD)	18.4 ± 13.44			21.02 ± 25.14			$t = -0.94$	122	.35

Table 4. Effectiveness of interventions.[a]

Overall effectiveness of the type of medication change on Global Assessment of Functioning(GAF) scores[b]				
	Pre-intervention GAF score	Post-intervention GAF score	ANCOVA, F	*p*
Monotherapy (*n*: 81)	33.54 (13.55)	59.51 (16.15)	0.19	.66
Combination (*n*: 77)	35.58(13.23)	59.61 (12.72)		
Overall effectiveness of the type of medication change in suppressing positive psychotic symptoms[c]				
	Mean	SD	*t* (df)	*p*
Switch (*n*: 83)	3.35	0.99	0.53 (162)	.60
Combination (*N*: 81)	3.27	0.90		

[a]Data are weighted to account for survey non-response. Numbers vary because of missing data.
[b]Possible scores range from 1 to 100, with lower scores indicating more severe impairment.
[c]As measured by a Likert scale. Possible scores range from 1 to 5, with higher scores indicating greater effectiveness.

treatment with the psychiatrist, history of hospitalization, and suicide.

Patients currently on monotherapy were more likely to have received combination therapy immediately before the change, compared to those currently on combination of antipsychotics ($p = .00$). Patients who are currently on combination were more likely to have been on monotherapy immediately before the change ($p = .00$).

Outcome of interventions

There was no difference between treatment groups, with respect to overall effectiveness of the type of medication change in relieving positive psychotic symptoms (M = 3.35, SD = 0.99 and M = 3.27, SD = 0.9) for switch and combination groups, respectively; t (162) = 0.53, $p = .60$) (Table 4).

After adjusting for pre-intervention GAF scores, there was no significant difference between two treatment groups on post-intervention scores of GAF ($F = 0.19$, $p = .66$). There was a strong relationship between the pre-intervention and post-intervention scores of GAF test ($p = .00$) indicating the limited benefit of either method on improvement of functioning.

Discussion

This present study found that almost equal number of prescribers chose monotherapy and combination of antipsychotics as a way of managing treatment resistance in schizophrenia and that augmentation and high-dose strategies were preferred less often. In a similar survey carried out in the US, looking into only treatment-resistant cases, 33% of cases were on combination therapy comparing to 46.1% in this sample [19]. Although the frequency of antipsychotic polypharmacy was found to vary according to patient, illness, setting and provider variables, rates in schizophrenia commonly were reported to range from 7% to 50% [13,20]. Given that our focus was on resistant cases only, the rate of combination in the present survey is not very far from what was reported in other studies. National studies, though not in particular on resistant cases, reported multiple antipsychotic uses from 38.2% to 64.7% in patients with schizophrenia in general [15–17].

It is quite possible that psychiatrists inherited some of these combination cases, as they reported that 61.6% of them were already on combination before the change they made. Despite this, they managed to move some patients from combination to monotherapy, as the ratio of patients on monotherapy increased from 28.7% to 40.1% in the present study after the change in medication regime. The study also revealed that those switched to monotherapy were reported to be more likely on combination immediately before the change. The reverse was also true that those commenced on combination were more likely to have been on single antipsychotic immediately before the change. This indicates that psychiatrists moved between monotherapy and combination when one failed to ameliorate the resistant symptoms.

Studies and guidelines recommend introduction of clozapine as the treatment of choice for treatment-resistant cases due to its superior efficacy. In certain cases of non-response to clozapine, the use of other second-generation antipsychotics, augmentation strategies with antidepressants and/or mood stabilizers, combination of antipsychotics and electroconvulsive therapy have been suggested as treatment alternatives, however, with limited evidence for their efficacy [2, 21–23]. Despite this, it was reported that clinicians do often try other approaches before clozapine prescription and there could be long delays before prescription of clozapine [24,25]. In the present study, only 48.3% of the patients with TRS were reported to be currently on clozapine, which shows that majority of clinicians avoided prescribing clozapine despite the guidelines. Our result is line with the existing literature. In a recent review which investigated international trend for clozapine use in 17 countries, it was concluded that while clozapine use has increased in most studied countries over recent years, clozapine is still underused in many countries and clozapine utilization patterns differed significantly between these countries [26]. For example, a recent Canadian study, based on physician drug recommendation from 2005 to 2009, showed a 48% increase in clozapine recommendations over a 5-

year period [27]; however, a more recent study reported that 68% of outpatients had tried three or more antipsychotics before switching to clozapine [28]. Data from 60% of the mental health trusts in England showed that only 30% of those eligible were actually receiving clozapine [29]. In contrast, clozapine utilization in Australia seems to be more appropriate with a percentage as high as 51% of clozapine use in TRS [30]. There have been some publications on prescription of clozapine in Turkey with an aim to promote and encourage its utilization in appropriate cases by providing an updated guide for psychiatrists who are over cautious about clozapine, which can hopefully make a positive influence on the prescribing patterns in Turkey [31,32].

In the present study, there were no prescriber-related factors associated with the choice of monotherapy or combination strategies. There was no relation between psychiatrist's clinical experience, job description (academic vs. non-academic, inpatient vs. outpatient setting) continuous professional development, knowledge of guidelines and their approach to treatment. This can raise the issue of psychiatrists relying more on their clinical experience than on guidelines. As there was no effect of age/experience of prescribers on the choice of prescription, it can be speculated that prescription habits may get inherited from the senior clinicians. In a similar survey done in the US, it was found out that psychiatrists who added rather than switched antipsychotics reported more frequent attendance at educational programmes sponsored by pharmaceutical companies [19]. There was no evidence of influence of pharmaceutical industry on the choice of treatment in this sample.

There appeared to be no significant association between the patient/illness characteristics and the pharmacological approach taken by the psychiatrists in this survey. This could perhaps be attributed to the fact that this survey focused only on resistant cases. In a critical review of antipsychotic polypharmacy which summarized the data from various surveys of psychiatrists on prescription habits, there were various factors revealed in relation to polypharmacy including patient's being male, young, single, unemployed, having severe psychopathology, residual psychotic symptoms, poor cognitive function, poor insight, and psychiatric comorbidity. Treatment in a psychiatric hospital, being an inpatient, involuntary admission, frequent admissions and treatment with a depot antipsychotic were among the other factors indicated by prescribers [33].

In terms of efficacy, no difference was found between the monotherapy and combination group in either relieving positive symptoms or improving functioning. This finding is consistent with the existing literature. Most studies did not report any improvement in schizophrenia symptoms with combining two antipsychotics [13,33]. In a study done with 158 patients in Turkey, no difference was reported between mono or combined therapy groups in terms of Positive and Negative Syndrome Scale (PANSS) scores [15]. In another study in Turkey (N:92), the quality of life was reported to be poorer with more side effect burden in polypharmacy group as compared to those receiving monotherapy [14].

There is some debate around the possible benefits of combining antipsychotics in certain conditions. In a nationwide Hungarian study, they found advantage of polypharmacy over monotherapy in terms of mortality and hospitalization suggesting better protection during exacerbation of psychotic symptoms [34]. Again, there is some evidence that adjunctive use of aripiprazole can fully or partially ameliorate prolactin elevation and metabolic side effects [35,36].

As it is the case in all surveys, the present study has some limitations. Although comparable to the previous studies, the sample size is small; therefore, it might not have represented the general prescribing patterns. There might also be a recall bias, given that information collected relied on the memory of participants, rather than investigating the actual patient files. It may also be subject to a selection bias in relation to both participating psychiatrists and the cases selected by them. Although we did our best to represent the psychiatrists in Turkey as much as possible, those who responded could be different from those who did not participate in the survey. It is also probably easier to link clozapine with resistant cases and report them, and therefore, it is likely that use of clozapine is over-represented in this study.

This is the first study looking into prescription habits of psychiatrists in Turkey for TRS cases. Although polypharmacy is found to be a common practice similar to other parts of the world, there seemed to be a comparably good ratio of clozapine utilization and attempts of switching to monotherapy among the prescribers. There remained many unanswered questions before discarding the idea of potential links between patient/prescriber characteristics and the preferred treatment regimens. Future studies on larger samples are required to correlate prescriber's perception and reports with actual behaviour.

Conclusion

The reluctance of practitioners to prescribe clozapine for management of TRS appears to be a prevalent issue among psychiatrists in Turkey, similar to practice in other parts of the world. Further studies are required to investigate possible factors associated with underusage of clozapine in more detail. Appropriate measures need to be identified and employed in order to address concerns that prescribers may have about clozapine prescription.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Serhat Çıtak http://orcid.org/0000-0003-1754-8307

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