

## Prescribing Clozapine in the MENA Region: The Perspective and Practice of Psychiatrists

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### وصف كلوزابين في منطقة الشرق الأوسط وشمال إفريقيا: وجهات نظر وممارسات الأطباء النفسيين

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#### Abstract

Clozapine is recommended as first-line treatment for treatment-resistant schizophrenia (TRS). Despite its established position in all international guidelines, prescribing and utilization rates of clozapine have consistently been low among psychiatrists. The primary aim of the current study was to survey psychiatrists in the Middle East and North Africa (MENA) region on clozapine prescription patterns and practices, attitudes towards the medication, and perceived barriers and facilitators for prescribing. Data were collected from 17 of the 21 countries belonging to the MENA region via an online questionnaire. The majority of participants stated that the most common indication for clozapine was TRS. While most reported high levels of expertise with clozapine and rated it as an effective treatment, only 53.1% used it as their first-line treatment. The main stated barriers were concerns over patients' poor compliance, the burden of regular blood testing, and the associated side effects. Years of practice and the setting of practice did not influence prescribing attitude and behavior. This study confirms that psychiatrists in the MENA do not diverge from the norm of clozapine under prescription. Structural reforms are required to establish services that have the capacity and experience to address clozapine prescribing.

**Keywords:** Clozapine, schizophrenia, Middle East, Africa, Northern, attitude, prescription

**Declaration of interest:** None

#### Introduction

Schizophrenia is one of the most debilitating psychiatric disorders affecting 20 million people worldwide. It is associated with a heavy burden on individuals and healthcare systems.<sup>1</sup> Treatment-resistant schizophrenia (TRS) is defined as persistent symptoms of schizophrenia causing functional impairment, following two treatment trials on different antipsychotic medication. This sizeable group of patients is estimated to constitute 20% to 30% of all schizophrenia diagnoses.<sup>2</sup>

Clozapine remains the first-line treatment and the only FDA-approved drug for TRS despite decades of advances in psychopharmacology. Evidence supporting the superiority of clozapine over all other antipsychotics in the management of TRS has been accumulating.<sup>3-5</sup> Clozapine has also been shown to decrease hospitalization rates and mortality rate of patients with schizophrenia.<sup>6,7</sup>

Despite the established position of clozapine in all international guidelines, prescribing and utilization rates of this drug have consistently been low among psychiatrists. Studies report low rates in countries with very diverse socio-economic profiles and health systems,

including New Zealand, England, Denmark, India, the Middle East, and the United States.<sup>8-12</sup> This translates often into a substantial delay of four to ten years before clozapine initiation, which exposes patients to an unnecessary period of active psychosis.

This mismatch between the expectations for clozapine and the clinical reality is commonly attributed to three barriers: prescriber-related, patient-related, and system-related.<sup>13-15</sup> Prescriber-related barriers have included lack of personal experience, concerns about clozapine side effects, or less frequently lack of knowledge about the medication. Patient refusal of the prescription and monitoring of the medication is described as another obstacle. However, while studies exploring the attitudes of prescribers cite this reason as one of the most common barriers, patients taking clozapine do not consistently report greater dissatisfaction with the medication compared to other antipsychotics.<sup>16,17</sup> This barrier can thus be more related to prejudice on the part of the prescriber rather than the patients. Finally, the third barrier encompasses limited administrative and logistical support

deemed necessary for the safe prescription and monitoring of clozapine.

The Middle East and North Africa (MENA) region is an area that is not officially defined but is recognized by international organizations to most commonly encompass 21 countries. In this area, few studies have explored the phenomenon of the underuse of clozapine. However, recent studies published in Oman, Saudi Arabia, and Bahrain on the patterns of prescription of antipsychotics reveal widespread under-prescribing of clozapine.<sup>18-20</sup> A recent qualitative study exploring prescribing and

monitoring practices of clozapine in the Gulf countries concluded that although mental health professionals in the region were aware of the effectiveness and the efficacy of clozapine for TRS, there is a tendency to avoid its use until all other treatment options are exhausted.<sup>21</sup>

The primary aim of the current study was to survey psychiatrists in the MENA region on clozapine prescribing, their attitudes towards it, and perceived limitations. It also considered possible association between these factors and the characteristics of the prescribing psychiatrist.

## **Methods**

This cross-sectional study was conducted between September and December 2019 following Institutional Review Board Approval (ID: SBS-2018-0555).

### ***Study design and selection criteria***

In the absence of accessible official databases, qualified psychiatrists practicing in the 21 MENA countries were identified using a snowball sampling strategy relying on three primary methods with a view to reach the widest representative sample. When possible, national psychiatric associations were contacted with a request to disseminate the survey invitation. A second method was through ‘champions’ (the authors) in a number of countries using their networks of colleagues. A third method was through a thorough online search identifying psychiatrists in academic centers, public state hospitals and private practice. Email invitations and reminders to fill the anonymous online questionnaire hosted on LimeSurvey were sent to a total of 1031 psychiatrists. 340 of these participated but only 245 complete responses were included in the final data analysis. Apart from Mauritania, Syria, and the Sahrawi republic, all targeted countries were represented in our sample, keeping in mind the wide workforce discrepancies between countries.

### ***Questionnaire design and validity***

In the absence of a validated questionnaire addressing the primary research questions, a self-administered questionnaire was compiled by the authors based on a literature review of similar regional studies.<sup>11</sup> The questionnaire was independently reviewed by three experts on content validity. It included 37 multiple choice and scaled questions, available in English and French, to reflect at least one of the languages of higher medical education in most MENA countries. It was divided into

four sections: demographic and professional characteristics of participants; prescription patterns and practices; attitudes towards the medication; and perceived barriers and facilitators for prescribing.

### ***Statistical analysis***

The primary outcomes were analyzed and tabulated per their nature: frequency and percentages for categorical variables; means, standard deviations, and ranges for continuous variables.

For the analytical analysis, we first transformed our variables (Supplementary Table 1) to primarily reflect the adherence of psychiatrists to international clozapine prescription guidelines. We also mean-centered the years of practice variable to aid in interpretability.

We ran a generalized linear model with a binomial distribution in participants fully trained in one of the MENA countries (n=214) to investigate the effect of the number of years of practice post-training and the work setting on the dependent variables: prescribing clozapine as first-line for TRS, initiating clozapine after two failed trials, referring patients to another prescriber for initiation of clozapine, and reporting that the percentage of a prescriber’s patients who should be on clozapine and are not on it is less than 25%. In the model, we accounted for the fixed effect of a possible interaction between the number of years of practice and the work setting. We included the country of practice as a random effect to account for the clustering of data by country. Because the comparison of psychiatrists fully trained in MENA countries and psychiatrists trained outside was underpowered due to the small sample size of the latter group, we performed this analysis as a tertiary outcome by using a logistic regression.

## Results

### Descriptive analysis

#### Sample characteristics of participants

The demographic and professional characteristics of the participants are detailed in Table 1. 53.1% of participants

were men with a mean age of 39.57 (SD=8.936). The mean number of years in clinical practice was 9.89 years (SD=8.652). Most psychiatrists (87.3%) were fully trained in a MENA country and worked in a hospital setting (79.6%).

**Table 1.** Sample characteristics of the study population. SD: standard deviation; MENA: Middle East and North Africa

	Mean	SD	Range
<i>Age</i>	39.57	8.936	52
<i>Years in clinical practice</i>	9.89	8.652	41
		<b>n</b>	<b>%</b>
<i>Gender</i>	Male	130	53.1
	Female	115	46.9
<i>Psychiatry area of expertise</i>	Addiction	37	15.1
	Child and adolescent	31	12.6
	Consultation-liaison	15	6.1
	Geriatric	7	2.8
	Mood disorders	6	2.4
	Psychotic disorders	5	2.0
	Community	3	1.2
	Forensic	3	1.2
	Sexology	3	1.2
	Eating disorders	1	0.4
	Women's mental health	1	0.4
<i>Country of training</i>	Full training in MENA country	214	87.3
	Full or partial training in non-MENA country	31	12.6
<i>Country of practice</i>	Egypt	58	23.7
	Iran	35	14.3
	Tunisia	34	13.9
	Lebanon	25	10.2
	United Arab Emirates	25	10.2
	Oman	19	7.8
	Saudi Arabia	16	6.5
	Jordan	6	2.4
	Yemen	5	2
	Qatar	4	1.6
	Kuwait	3	1.2
	Libya	3	1.2
	Morocco	3	1.2
	Algeria	2	0.8
	Bahrain	2	0.8
Iraq	1	0.4	
Occupied Palestinian territory	1	0.4	

<b>Work setting</b>	Teaching hospital	90	36.7
	Public hospital	77	31.4
	Private clinic	46	18.8
	Private hospital	28	11.4
	Non-governmental organization	4	1.6

*Prescription patterns and practices of clozapine*

Most participants (86.5%) stated that the most common indication for their use of clozapine is TRS and 53.1% stated that their first-line treatment for TRS is clozapine; 53.5% consider starting clozapine after failure of two previous trials of antipsychotics. Figure 1a and 1b detail the initial and maintenance clozapine laboratory workup ordered by participants and the frequency of CBC monitoring, respectively.

A total 90.2% of participants stated they always, frequently, or occasionally combine clozapine with other antipsychotics; only 9.8% reported never using a combination while 69.8% reported rarely or never using electroconvulsive therapy (ECT) in patients maintained on clozapine. Supplementary Tables 2 and 3 summarize the participants' dosing patterns of clozapine and the management options of clozapine-related side effects, respectively.

*Attitudes, barriers, and facilitators of clozapine prescription*

A total 75.9% of participants rated their level of expertise in the prescription and management of clozapine as good or excellent; 20.4% rated it as fair and only; 3.7% rated it as poor while 74% felt that they were comfortable initiating clozapine by themselves; 45.3% of the psychiatrists estimated that more than 25% of their patients in whom clozapine is clinically indicated are not on it. Similarly, 75.5% noted that they often, frequently, or always see patients managed by other clinicians who would benefit from clozapine but are not receiving it.

Most participants rated clozapine as highly (46.9%) or moderately (49%) effective for the treatment of TRS. A total 63.3% reported high efficacy for the treatment of positive symptoms while only 10.6% reported high efficacy for negative symptoms.

A total 52.5% and 35% of participants respectively felt that their patients had a higher level or an equivalent level of satisfaction with clozapine as compared to other antipsychotics. Only 12.5% felt that their patients were less satisfied with clozapine. Table 2 lists the barriers and facilitators of the initiation of clozapine as reported by participants.

**Table 2.** Barriers and facilitators to the initiation of clozapine

<b>Barriers</b>		<b>N</b>	<b>%</b>
<b>Patient-related</b>	No commitment to frequent laboratory workup	172	70.2
	Fear of clozapine-related side effects	146	59.6
	History of poor medication compliance	141	57.6
	Lack of social support	113	46.1
	Reluctance from patient's caregiver	96	39.2
	Medical comorbidity	94	38.4
	Refusal to be admitted to hospital for dose titration	66	26.9
	Patient unconvinced of clozapine efficacy	32	13.1
	Concern about cost of treatment	30	12.2
<b>Prescriber-related</b>	Need for laboratory monitoring	176	71.8
	Concerns about blood dyscrasias	161	65.7
	Concerns about clozapine-related metabolic effects	102	41.6
	Concerns about other clozapine-related effects	67	27.3

	Concerns about risk of seizures	54	22
	Concerns about efficacy	9	3.7
<b>Healthcare system-related</b>	Need for hospital admission	67	27.3
	Lack of staff resources	30	12.2
	Administrative factors	28	11.4
	Cost of treatment	26	10.6
<b>Facilitators</b>		<b>N</b>	<b>%</b>
<b>Facilitating factors</b>	Additional staff resources	127	51.8
	Dedicated day-hospital placements	125	51
	Additional administrative support	99	40.4
	Dedicated hospital beds for dose titration	82	33.5

**Statistical analysis**

The generalized linear model applied in the case of psychiatrists with exclusive training in MENA countries does not support the work setting or the years of

independent clinical practice being determining factors in the practices and attitudes of psychiatrists towards clozapine (Table 3). In addition, exclusively-MENA trained psychiatrists did not differ from their peers in their practices and attitudes towards clozapine (Table 4).

**Table 3.** Effect of work setting and years of clinical practice on clozapine prescription practices in a generalized linear model in participants fully trained in MENA countries (N=214), depicted as odds ratio (p-value). TRS: treatment-resistant schizophrenia

	<b>Academic setting (1)</b>	<b>Inpatient setting (2)</b>	<b>Years in clinical practice</b>	<b>Years in clinical practice * Academic setting (1)</b>	<b>Years in clinical practice * Inpatient setting (2)</b>
<b>First-line treatment for TRS</b>	0.616 (0.265)	0.717 (0.437)	0.982 (0.657)	1.034 (0.208)	1.065 (0.544)
<b>Number of failed trials prior to initiation of clozapine</b>	0.854 (0.720)	1.216 (0.653)	0.984 (0.700)	1.041 (0.419)	1.008 (0.882)
<b>Referral to another prescriber</b>	0.965 (0.943)	0.841 (0.718)	0.962 (0.381)	1.109 (0.083)	1.058 (0.355)
<b>Number of patients with under prescription of clozapine</b>	0.846 (0.705)	0.578 (0.207)	1.080 (0.145)	0.098 (0.717)	0.880 (0.049)

**Table 4.** Logistic regression of clozapine prescription practices in participants with full training in MENA countries vs participants with full or partial training in a non-MENA country, depicted as odds ratio (p-value). TRS: treatment-resistant schizophrenia; MENA: Middle East and North Africa

	<b>Full training in MENA country vs full or partial training in non-MENA country</b>
<b>First-line treatment for TRS</b>	1.191 (0.656)
<b>Number of failed trials prior to initiation of clozapine</b>	1.525 (0.290)
<b>Referral to another prescriber</b>	1.948 (0.169)
<b>Number of patients with under prescription of clozapine</b>	0.930 (0.852)

## Discussion

In the current survey of 245 psychiatrists practicing in the MENA region, most participants estimated their level of expertise in the prescription of clozapine to be good or better. The majority recognized TRS as the most common indication for clozapine, demonstrating awareness of international recommendations,<sup>22</sup> and reported confidence in prescribing it, in line with findings from international surveys.<sup>12,15</sup> Most participants in our sample believed clozapine to be more effective than other antipsychotics in treating schizophrenia, in agreement with the international consensus.<sup>12,15, 23</sup> Up to 85% of participants felt that their patients who were prescribed clozapine were satisfied with the treatment.

Despite no obvious gaps in knowledge or experience related to clozapine, only half of our sample were prioritizing clozapine as a first-line treatment for TRS while a significant number reported that over 25% of patients who should be on it had not been initiated. Concerningly, our survey also notes a reluctance to refer patients to other psychiatrists for clozapine initiation and management. This could be explained by several factors, such as the absence of a mental health care system that would encourage cross referrals and the lack of a collaborative culture.

Instead, almost all psychiatrists acknowledged regularly combining antipsychotics.<sup>24</sup> While the reasons may differ, these findings are concordant with trends in several studies on clozapine underutilization carried out in other parts of the world.<sup>25</sup>

In the investigation of barriers to the adequate initiation of clozapine, three main obstacles seem to delay the prescription: concerns about poor medication compliance, the need for frequent blood tests and clozapine-related side effects. These concerns were noted by participants as both prescriber-related and patient-related barriers. Although this finding replicates previous regional studies,<sup>11,13</sup> surveys of patients' opinions of clozapine reveal a generally positive attitudes despite its associated inconveniences.<sup>17,26</sup> Patients on clozapine report satisfaction with the medication.<sup>16,17</sup> Among the side effects of clozapine, agranulocytosis is cited as the most concerning despite its low incidence rate.<sup>27</sup> On the other hand, participants in the current study identified the availability of additional staff resources and dedicated day-hospital placements as main factors that facilitate the initiation of clozapine, highlighting previously suggested approaches including the implementation of integrated clozapine clinics and advancing technologies for point-of-care hematologic monitoring.<sup>28</sup>

Our analysis does not identify a generational divide in clozapine prescription practices. It also does not support a difference between inpatient, outpatient, and academic settings despite an assumption that access to resources varies across sites. This finding adds to the argument that under-prescribing of clozapine is a complex multilayered phenomenon.<sup>23</sup> Finally, the analysis does not support the hypothesis that the patterns of prescription differ between psychiatrists who are trained in MENA countries and those trained outside the region. In fact, only a minority had received training abroad emphasizing the importance of local curriculums and influencers on practice.

The main limitations of this study include a relatively low response rate and the concentration of the majority of respondents in 7 of the 21 MENA countries. These limitations may restrict the generalizability of the findings to the entirety of the MENA region. The questionnaire was not validated and mainly based on a thorough literature review and expert opinion. Finally, the comparison between exclusively and non-exclusively MENA-trained psychiatrists was underpowered to detect a statistically significant difference between the two groups.

Despite these limitations, the current study is, to our knowledge, the first large scale study to explore clinical practice surrounding clozapine across a region comprising a large underserved population sharing culture, religion, and social contexts, but also common challenges to adequate mental health provision. The underuse of an established treatment with unique properties with an affordable cost has serious implications for several thousand patients and their families. This is particularly important when psychosocial approaches to psychosis are limited, the needed skilled workforce unlikely to be available in the near future, and specialist rehabilitation facilities all but nonexistent. Regional-based research constitutes a critical step to detecting and addressing barriers to the implementation of generalizable guidelines,<sup>29</sup> such as those related to clozapine in schizophrenia. By understanding the factors that influence the key decision makers - the prescribers in this case - targeted measures can be devised to effect change in attitude and behavior. This study confirms that psychiatrists in the MENA do not diverge from this norm. Underprescribing is consistent despite the availability of the medication in most surveyed countries, the clinicians' understanding of its mechanism and effectiveness, and a generally positive attitude towards its role. For knowledge and attitude to translate into increased confidence to prescribe requires clozapine to be championed across the

region, whether through the creation of regional or national guidelines on the treatment of psychosis, the dissemination of local research, and training modules that recognize the clinical reality specific to each country. Education of the patient and their families is also an important facilitating step. In parallel, structural reforms are required to establish specialist community services that have the capacity and the experience in addressing the complex needs of patients with treatment resistant

psychosis. Such services have emerged in countries such as the United Arab Emirates and Lebanon,<sup>30</sup> but remain limited in scope. In addition, while not explored in our survey, the enactment of modern mental health legislation in these countries could play a role in encouraging and supporting clinical teams in providing as many treatment options as possible, including clozapine, for those suffering from the burden of treatment resistance psychotic disorders.

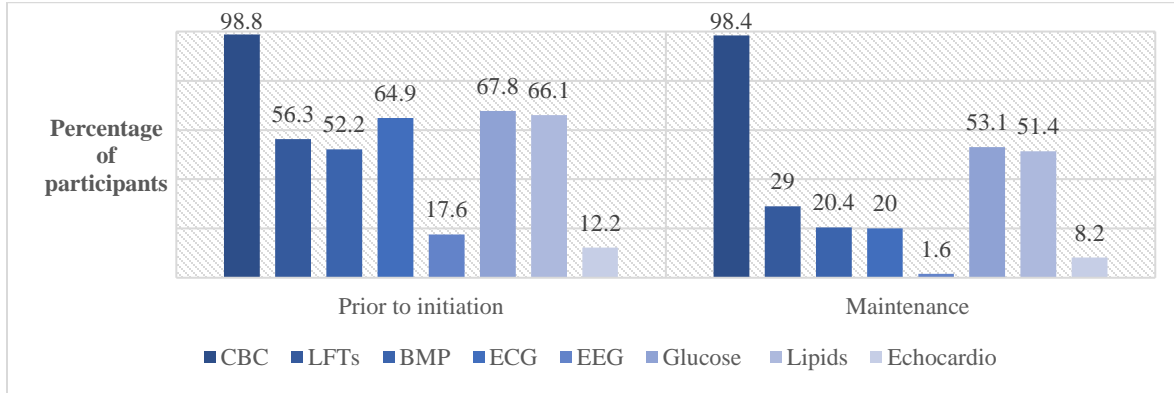


Figure 1a. Workup ordered prior to initiation and during maintenance treatment with clozapine

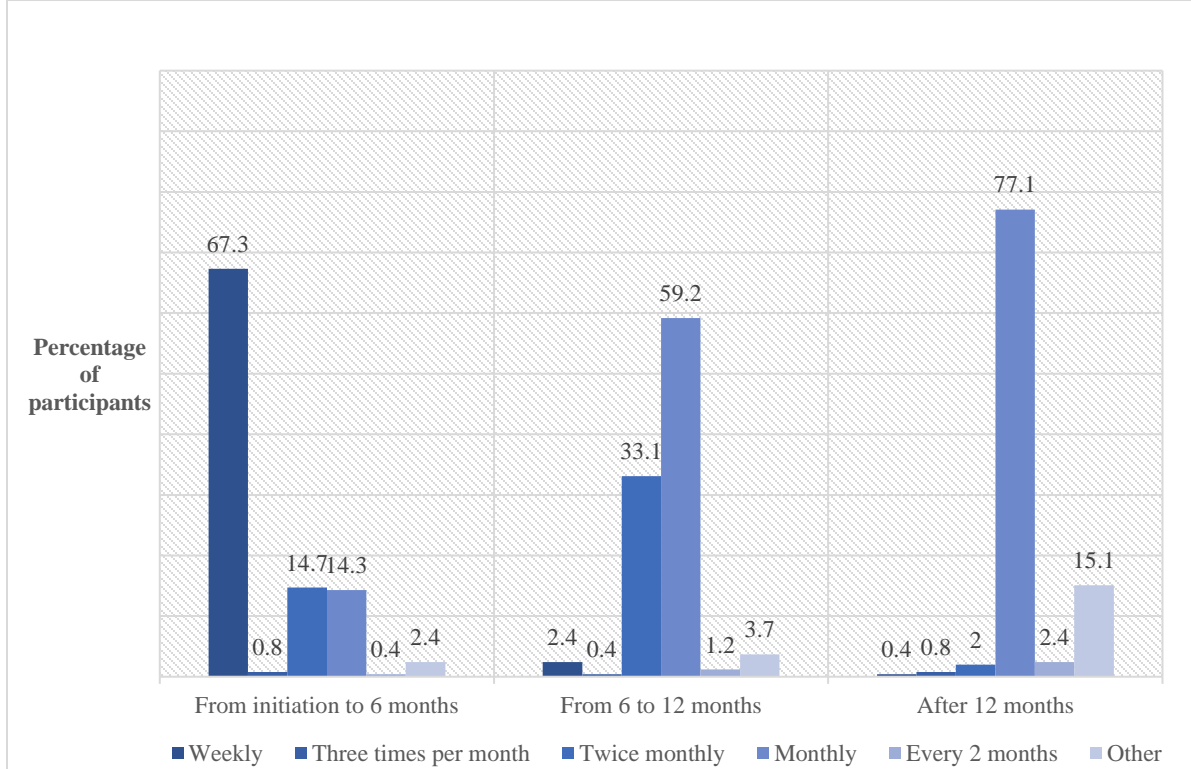


Figure 1b. Frequency of CBC monitoring during clozapine treatment

Supplementary material

Supplementary Table 1. Transformation of dependent and independent variables

<i>Dependent variables</i>					
<i>First-line treatment for TRS</i>			<i>Number of failed trials</i>		
<i>Clozapine</i>	→	Prescribing clozapine as per the guidelines	2	→	Two trials as per the guidelines
<i>ECT</i>	→	Not prescribing clozapine (not following the guidelines)	1	→	More or less than two trials (not following the guidelines)
<i>Combination of antipsychotics</i>			3		
<i>Combination of antipsychotics with clozapine</i>			4		
			>4		
<i>Referral to another prescriber*</i>			<i>Number of patients with underprescription of clozapine**</i>		
<i>Always</i>	→	Refer	<25%	→	<25%
<i>Frequently</i>					
<i>Often</i>					
<i>Rarely</i>	→	Not refer	25%-50%	→	>25%
<i>Never</i>			50%-75%		
			>75%		
<i>Independent variables</i>					
<i>Main work setting</i>					
<i>NGO</i>		→		Outpatient setting	
<i>Private clinic</i>		→		Inpatient setting	
<i>Private hospital</i>		→		Academic setting	
<i>Public hospital</i>		→			
<i>Teaching/University hospital</i>		→			

\* Answers to the question: “How often do you choose to refer patients to another prescriber for initiation of clozapine?”

\*\*Answers to the question: “What percentage of your patients in which clozapine is clinically indicated are not on it?”



**Supplementary Table 2.** Dosing practices of clozapine

<p><b>* Answers to the question: “How often do you choose to refer patients to another prescriber for initiation of clozapine?”</b></p>	<p><b>* Answers to the question: “How often do you choose to refer patients to another prescriber for initiation of clozapine?”</b></p>	<p><b>* Answers to the question: “How often do you choose to refer patients to another prescriber for initiation of clozapine?”</b></p>	<p><b>* Answers to the question: “How often do you choose to refer patients to another prescriber for initiation of clozapine?”</b></p>
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QD=once daily; BID=twice daily

**Supplementary Table 3.** Management of side effects of clozapine

		n	%
Sialorrhea	Stop clozapine	5	2
	Reduce dose	71	29
	Do nothing	56	22.9
	Wait for tolerance	100	40.8
	Add amitriptyline	54	22
	Add clonidine	33	13.5
	Add glycopyrrolate	14	5.7
	Add trihexyphenidyl	45	18.4
Constipation	Stop clozapine	2	0.8
	Reduce dose	42	17.1
	Do nothing	14	5.7
	Wait for tolerance	36	14.7
	Dietary modifications	214	87.3
	Add laxatives	160	65.3
Sedation	Stop clozapine	5	2
	Reduce dose	84	34.3
	Change timing	148	60.4
	Move to bedtime	196	80
	Do nothing	13	5.3
	Wait for tolerance	76	31

	Add stimulant	3	1.2
	Add SSRI	5	2
Neutropenia	Stop clozapine	215	87.8
	Reduce dose	37	15.1
	Do nothing	6	2.4
	Prescribe Lithium	41	16.7
	Prescribe G-CSF	13	5.3
	Consult specialist	9	3.7

SSRI=selective serotonin reuptake inhibitors; G-CSF=Granulocyte-colony stimulating factor.

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## المخلص

يوصى باستخدام كلوزابين كعلاج من الدرجة الأولى لمرض الفصام المقاوم للعلاج. على الرغم من موقعه الراسخ في جميع الإرشادات الدولية، إلا أن معدلات وصف واستخدام كلوزابين لا تزال منخفضة بين الأطباء النفسيين. الهدف الأساسي من هذه الدراسة كان إجراء مسح للأطباء النفسيين في منطقة الشرق الأوسط وشمال إفريقيا لمعرفة أنماطهم في وصف كلوزابين، ومواقفهم تجاه الدواء، والعوائق والميسرات لوصفه. تم جمع البيانات من 17 دولة من أصل 21 دولة تنتمي إلى منطقة الشرق الأوسط وشمال إفريقيا من خلال استبيان عبر الإنترنت. ذكر غالبية المشاركين أن أكثر المؤشرات شيوعاً لاستخدام كلوزابين هي الفصام المقاوم للعلاج. في حين أن معظم المشاركين أبلغوا عن مستويات عالية من الخبرة مع كلوزابين وصنفوه على أنه علاج فعال للفصام المقاوم للعلاج، أعلن فقط 1، 53٪ عن استخدامه كخط العلاج الأول. العوائق الرئيسية في وصف كلوزابين هي المخاوف بشأن امتثال المرضى للدواء، عبء اختبارات الدم المنتظمة، والآثار الجانبية. سنوات ومكان الممارسة الطبية لم تؤثران في وصف الدواء أو السلوكيات المتعلقة به. تؤكد هذه الدراسة أن الأطباء النفسيين في منطقة الشرق الأوسط وشمال إفريقيا لا يختلفون عن المعيار العالمي في عدم اعتماد وصف كلوزابين. العديد من الإصلاحات الهيكلية مطلوبة من أجل إنشاء خدمات لديها القدرة اللازمة لوصف كلوزابين.

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