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Original article

Patients' and primary carers' views on clozapine treatment for schizophrenia: A cross-sectional study in Qatar

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ABSTRACT

Subjective views of clozapine treatment among patients with schizophrenia in the Middle East and North African MENA Region have not previously been assessed. Globally, few studies have assessed the views of carers to clozapine treatment. We conducted a cross-sectional survey, using a clinician administered structured interview, of patients with schizophrenia/schizoaffective disorder prescribed clozapine in Qatar, and their primary carers. Participants were asked to rate clozapine against prior their antipsychotic treatment in terms of specific benefits and side effects. Forty-two patients and 33 carers participated in the study. Of the patients, two thirds were male, approximately half were Qatari and the mean age was 33.9 years. Patients and carers rated clozapine as superior to prior antipsychotic treatment on all 7 potential benefits inquired about. The greatest perceived benefit was improved mood. Patients rated clozapine as less likely to cause extrapyramidal side effects but more likely to cause 18 other potential side effects compared to prior antipsychotic treatment, with the greatest difference being for nocturnal salivation, increased appetite, and constipation. Nearly half of patients (48 %) and two thirds of carers (64 %) stated that they would have preferred to start clozapine earlier in their illness. Sixty percent of patients and 37 % of carers regarded the information that they had received from health professionals on clozapine as inadequate. Less than half of patients and approximately-two thirds of carers had adequate knowledge of haematological monitoring for clozapine. Generally, there were significantly positive correlation between patients and carers regarding the overall side effects of clozapine treatment. Likewise, improvement in hearing voices paranoid thoughts correlated with improved quality of life. In summary, the results show that patients and carers appreciate the benefits of clozapine despite its side effects being problematic. The results support clozapine being offered earlier in treatment and services providing more information on clozapine to patients and carers.

1. Introduction

Schizophrenia is a common and serious psychiatric illness with a lifetime risk of approximately 1 % (Perälä et al., 2007). It is the eighth leading cause of disability worldwide among young adults and is associated with high indirect costs due to unemployment and lost productivity associated with caregiving (World Health Organization, 2001). Antipsychotic drugs are of central importance in the management of schizophrenia. However, 20 to 30 % of patients do not respond adequately to antipsychotic medication (excluding clozapine) and have persistent symptoms (Elkis and Buckley, 2016). Clozapine is the only drug approved for Treatment Resistant Schizophrenia (TRS) which is defined as continuing symptoms despite trials of at least two different antipsychotic drugs of adequate dose and duration (Galletly et al., 2016;

Abbreviations: RCTs, Randomised Controlled Trials; NNH, Number Needed to Harm; MENA, Middle East and North Africa; HMC, Hamad Medical Corporation; IRB, Institutional Review Board; MRC, Medical Research Center; WCC, White Cell Count; GASS, Glasgow Antipsychotic Side-effects Scale.

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Keepers et al., 2020; NICE, 2014). A *meta*-analysis, with 21 randomised controlled trials (RCTs) and 2364 participants, showed that clozapine was more efficacious than other antipsychotics in treating positive symptoms in both the short and long term in people with TRS (Siskind et al., 2016). Approximately 40 % of people with TRS have a clinically meaningful response to clozapine if the trial is of sufficient duration (Siskind et al., 2017). Guidelines for schizophrenia are consistent in recommending clozapine as the drug of choice for TRS (Galletly et al., 2016; Keepers et al., 2020; NICE, 2014).

Side effects of clozapine include sedation, excess salivation, neutropenia, seizures, weight gain and metabolic dysregulation (Miller, 2000). A *meta*-analysis found that 8 of 13 adverse effects were more prevalent with clozapine than with comparator antipsychotics with a number needed to harm (NNH) that ranged from 4 for sialorrhoea to 19 for fever and nausea/vomiting (Siskind et al., 2016). The pharmacokinetic interaction between the aromatic hydrocarbons in cigarette smoke and clozapine may necessitate a higher dose of clozapine in smokers compared to non-smokers (Tsuda et al., 2014).

Despite clozapine's unique efficacy and place in evidence-based guidelines, the views of patients prescribed clozapine have only been assessed in a small number of studies (Qurashi et al., 2015; Waserman and Criollo, 2000; Verma et al 2021). This is despite health care professionals being encouraged to consider the perspective of patients and involve them in treatment decisions (Say and Thomson, 2003). The experience of patients gives context to other sources of clinical data and can assist management (Rand et al., 2019). A consistent finding across studies that have assessed patients' views is improved satisfaction with clozapine compared to prior antipsychotic treatment (Qurashi et al., 2015; Waserman and Criollo, 2000; Verma et al., 2021). Specific benefits reported by patients include improved thinking, mood, alertness and adherence with treatment (Waserman and Criollo, 2000).

The existing research on patients' views of clozapine has limitations. One UK study was restricted to male inpatients at a secure hospital (Qurashi et al., 2015) and so the results may not be generalizable to community-based adult patients, the group that accounts for most people prescribed clozapine. In addition, no studies have evaluated the views of patients prescribed clozapine in the Middle East and North Africa (MENA) region. Differences in public perception of mental illness, culture, and the provision of psychiatric services between Western countries and the MENA region may influence the attitudes of patients and their carers to clozapine. For example, the MENA region, compared to the West, is associated with greater mental health stigma (Krendl and Pescosolido, 2020), a higher proportion of patients living with family members (Alyafei et al., 2021), less developed community psychiatry services (Wadoo et al., 2021), and less availability of clozapine haematological and clozapine plasma level monitoring. Finally, psychiatrists in the MENA region may have greater concerns about managing side effects of clozapine (Ismail et al., 2019).

The primary aim of this study was to investigate the views of patients in Qatar, and their primary carers, to clozapine. As far as we know, this is the first study assessing the attitudes of patients and carers to clozapine conducted in the MENA region. In more detail, the study aimed to gather the views of patients, and their carers, to clozapine in terms of:

- Side effects experienced
- Benefits experienced
- Nature and satisfaction with clozapine-related information received from mental health services
- Knowledge of haematological monitoring (and for patients the interaction of smoking with clozapine effectiveness)

In addition, patients were asked about the quality of support they currently received from their clinical team related to taking clozapine. The study was restricted to patients with schizophrenia, schizoaffective disorder or delusional disorder who were currently prescribed clozapine.

2. Material and methods

2.1. Setting and recruitment

The study design was a cross sectional study with data gathered using a clinician administered structured interview. The study was conducted in Hamad Medical Corporation (HMC) which is the main provider of Mental Health Services in Qatar and runs the country's only dedicated psychiatric hospital. All prescriptions for clozapine in HMC are issued by the psychiatric hospital pharmacy. The hospital pharmacy records were reviewed to identify all HMC patients who were prescribed clozapine and met the inclusion/ exclusion criteria during the period 1st January and 31st December 2020. Eligible patients were informed about the study and given a study information leaflet and asked if they wished to participate in the study. If they declined, they were not contacted further. If they agreed, an appointment for a face-to-face research assessment was arranged. At that appointment, the study was explained again and if the patient still wished to take part signed consent was taken and the patient proceeded to complete the assessment.

2.2. Inclusion and exclusion criteria

The patient inclusion criteria were:

1. Age 18 to 65 years.
2. Diagnosis of schizophrenia, schizoaffective disorder or delusional disorder recorded in the electronic patient record.
3. Current prescription of clozapine, either as a monotherapy or in combination with another antipsychotic medication with duration of treatment with clozapine of at least 4 months.
4. Patient speaks English or Arabic.
5. Patient is able to give informed consent.
6. Patient is currently under the care of the HMC Psychiatric Department.

A review of the literature showed that recommendations regarding the optimal duration of a trial of clozapine ranged from 2 months (Conley et al., 1997) to 6 months (Barnes et al., 2020). The entry criteria of $\geq$ 4 months of treatment with clozapine was chosen to be mid-way in this range and to allow the data to represent the views of patients who had completed a reasonable trial of clozapine (i.e. 4 months) and opted to continue treatment beyond this. As long as the inclusion criteria were met, there were no exclusion criteria.

2.3. Patient assessment

Patient were interviewed by a research psychiatrist. The patient interview involved participants completing a battery of 28 questions, rated on a 5-point Likert scale, which asked them to compare clozapine with their last prescribed antipsychotic in terms of side effects (21 items) and effectiveness (7 items) (see Table 2 and 3). The Likert scale options were that clozapine was Much worse (1), Worse (2), No different (3), Better (4) or Much better (5) in comparison to the last antipsychotic. This section of the instrument was adapted from questions originally to investigate patients' views of clozapine treatment in the USA (Waserman and Criollo, 2000)

Table 1
Sociodemographic characteristics of participating patients (n = 42).

Characteristic	n (%)
Sex	
Female	14 (33.3 %)
Male	28 (66.7 %)
Age (years)	
Mean	33.9
Median	33
SD	10.31
Range	47 (19–65)
Nationality	
Qatari	19 (45.2 %)
Non-Qatari	23 (54.8 %)
Marital Status	
Single	33 (78.6 %)
Married	7 (16.7 %)
Divorced and not living alone	1 (2.4 %)
Divorced and living alone	1 (2.4 %)
Living status	
At home	34 (81.0 %)
Community placement	5 (11.9 %)
Long-stay ward	3 (7.1 %)
Diagnosis	
Schizophrenia	37 (88.1 %)
Schizoaffective disorder	5 (11.9 %)
Others	0 (0 %)
Length of illness	
<1 year	0 (0 %)
1 to < 2 years	0 (0 %)
2 to < 5 years	9 (21.4 %)
5 to < 10 years	15 (35.7 %)
10 years or more	18 (42.9 %)
Duration being on Clozapine	
<1 year	4 (9.5 %)
1 to < 2 years	10 (23.8 %)
2 to < 5 years	17 (40.5 %)
5 to < 10 years	10 (23.8 %)
10 years or more	1 (2.4 %)

Table 2
Sociodemographic characteristics of participating carers (n = 33).

Characteristics	n (%)
Sex	
Female	14 (42.4 %)
Male	19 (57.6 %)
Age (years)	
Mean	49.97
Median	50.00
SD	14.56
Range	60.00
Nationality	
Qatari	8 (24.2 %)
Non-Qatari	25 (75.8 %)
Relationship to the patient	
Husband or wife	5 (15.2 %)
Parent	18 (54.5 %)
Primary Nurse	6 (18.2 %)
Sibling	3 (9.1 %)
Son or daughter	1 (3.0 %)
Do you live with the patient?	
Yes	3 (9.1 %)
No	30 (90.9 %)

and later adapted for use in a similar study in the UK (Qurashi et al., 2015).

A series of additional questions, with set response options, were asked to determine the patient's views on the quality of the information they had received from mental health services about clozapine and the quality of the support received from their clinical team related to taking clozapine.

The assessment concluded with a structured interview to determine participant's knowledge of the interaction of clozapine with smoking and participant's knowledge of blood monitoring during clozapine treatment. The interviewing doctor categorized the participant's level of knowledge using set criteria (see Tables 5, 6 and 7). A structured interview, rather than asking patients to select answers from range of fixed response options, was used to assess knowledge in both areas as it was felt this was a more valid way to determine participant's knowledge given the complexity of these areas. Where necessary the clinicians provided prompts to help explore the patient's knowledge.

The assessment instrument was devised by the research team based on their knowledge and experience of prescribing clozapine and a review of the existing literature including previous studies assessing patients' views on clozapine (Qurashi et al., 2015; Waserman and Criollo, 2000; Verma et al 2021). Most interviews were conducted in Arabic, the remainder were conducted in English by bilingual member of the research team. The information gathered at the assessment interview was supplemented by extracting basic sociodemographic and clinical information from the electronic patient records. This included employment status, nationality, diagnosis, length of psychotic illness, current medication and previous antipsychotic treatment.

2.4. Carer assessment

Each patient was asked to nominate the relative or friend most involved with their care (referred to from now on as the 'carer'). If the carer agreed to take part, they completed a short interview with a research psychiatrist that assessed their views about the patient's response to clozapine. The carer assessment was shorter than the patient assessment. Common aspects of both the patient and carer assessments included 7 items on the effectiveness of clozapine, 3 items on the quality of information provided by the health service on clozapine and 3 items that assessed knowledge related to hematological monitoring. In addition, carers were asked to rate 3 potential side effects of clozapine (salivation, weight gain and sedation) and provide a global rating of overall side effects of clozapine as experienced by the patient they cared for i.e. carers were asked about fewer side effects than patients. Carers, like patients, rated the effectiveness and side effects of clozapine in comparison to the last prescribed antipsychotic. Patients and carers were interviewed separately.

2.5. Statistical analysis

Categorical data were presented as counts and percentages (proportions) and continuous data were presented as rates, means and standard deviations. For both patient and carer data, mean scores were calculated for the 7 potential benefits of clozapine and its side effects. To recap, for assessment of side effects comprised a global measure of total side effect burden plus 21 specific side effects for patients, whereas for carers it comprised a global measure of total side effect burden plus 3 specific side effects. The normality assumption of the data was evaluated using the Shapiro–Wilk test. Given the nonnormality of the data, correlations between patients and carers views were evaluated using Spearman's correlation coefficients.

2.6. Ethical issues

The study received approval from the HMC Institutional Review Board (IRB) (MRC-01–19-352). Data was managed in keeping with

Table 3
Patients' views of clozapine's benefits and side effects compared to prior antipsychotic treatment (n = 42).

ITEM	Number of responses					Mean rating*
	Much worse [1] n (%)	Worse [2] n (%)	No difference [3] n (%)	Better [4] n (%)	Much better [5] n (%)	
Hearing voices	1 (2.4 %)	0 (0 %)	14 (33.3 %)	10 (23.8 %)	17 (40.5 %)	**4.00**
Other unusual experiences	1 (2.4 %)	2 (4.8 %)	25 (59.5 %)	6 (14.3 %)	8 (19.0 %)	**3.43**
Paranoid thoughts	1 (2.4 %)	0 (0 %)	15 (35.7 %)	9 (21.4 %)	17 (40.5 %)	**3.98**
Thinking more clearly	2 (4.8 %)	3 (7.1 %)	13 (31.0 %)	13 (31.0 %)	11 (26.2 %)	**3.67**
Mood	1 (2.4 %)	2 (4.8 %)	6 (14.3 %)	16 (38.1 %)	17 (40.5 %)	**4.10**
Improving your quality of life	1 (2.4 %)	2 (4.8 %)	12 (28.6 %)	10 (23.8 %)	17 (40.5 %)	**3.95**
	2 (4.8 %)	1 (2.4 %)	16 (38.1 %)	11 (26.2 %)	12 (28.6 %)	**3.71**
Having more interest and being more active						
Nocturnal salivation	15 (35.7 %)	10 (23.8 %)	14 (33.3 %)	3 (7.1 %)	0 (0 %)	**2.12**
Daytime salivation	3 (7.1 %)	3 (7.1 %)	32 (76.2 %)	4 (9.5 %)	0 (0 %)	**2.88**
Weight gain	8 (19.0 %)	12 (28.6 %)	15 (35.7 %)	7 (16.7 %)	0 (0 %)	**2.50**
Daytime sedation	6 (14.3 %)	7 (16.7 %)	20 (47.6 %)	6 (14.3 %)	3 (7.1 %)	**2.83**
Dry Mouth	0 (0 %)	5 (11.9 %)	35 (83.3 %)	2 (4.8 %)	0 (0 %)	**2.93**
Stiffness	2 (4.8 %)	0 (0 %)	31 (73.8 %)	5 (11.9 %)	4 (9.5 %)	**3.21**
Jerky movements of arms or legs	1 (2.4 %)	3 (7.1 %)	32 (76.2 %)	3 (7.1 %)	3 (7.1 %)	**3.10**
Other abnormal movements	1 (2.4 %)	4 (9.5 %)	29 (69.0 %)	4 (9.5 %)	4 (9.5 %)	**3.14**
Sweating	1 (2.4 %)	4 (9.5 %)	36 (85.7 %)	1 (2.4 %)	0 (0 %)	**2.88**
Dizziness	5 (11.9 %)	4 (9.5 %)	29 (69.0 %)	2 (4.8 %)	2 (4.8 %)	**2.81**
Wetting yourself at night	3 (7.1 %)	3 (7.1 %)	33 (78.6 %)	3 (7.1 %)	0 (0 %)	**2.86**
Wetting yourself in the daytime	2 (4.8 %)	0 (0 %)	39 (92.9 %)	1 (2.4 %)	0 (0 %)	**2.93**
Blurred vision	2 (4.8 %)	4 (9.5 %)	35 (83.3 %)	0 (0 %)	1 (2.4 %)	**2.86**
Palpitations	3 (7.1 %)	2 (4.8 %)	36 (85.7 %)	1 (2.4 %)	0 (0 %)	**2.83**
Constipation	5 (11.9 %)	12 (28.6 %)	24 (57.1 %)	0 (0 %)	1 (2.4 %)	**2.52**
Nausea	2 (4.8 %)	6 (14.3 %)	30 (71.4 %)	3 (7.1 %)	1 (2.4 %)	**2.88**
Abdominal pain	2 (4.8 %)	5 (11.9 %)	33 (78.6 %)	2 (4.8 %)	0 (0 %)	**2.83**
Breathing problems	3 (7.1 %)	4 (9.5 %)	35 (83.3 %)	0 (0 %)	0 (0 %)	**2.76**
Tiredness	3 (7.1 %)	13 (31.0 %)	21 (50.0 %)	2 (4.8 %)	3 (7.1 %)	**2.74**
Headaches	0 (0 %)	4 (9.5 %)	37 (88.1 %)	1 (2.4 %)	0 (0 %)	**2.93**
Increased appetite	5 (11.9 %)	14 (33.3 %)	20 (47.6 %)	2 (4.8 %)	1 (2.4 %)	**2.52**
Overall side-effects	2 (4.8 %)	8 (19.0 %)	20 (47.6 %)	7 (16.7 %)	5 (11.9 %)	**3.12**

* Ratings greater than 3 indicate that the variable was regarded as better during clozapine treatment compared to treatment with the previous antipsychotic (i.e. a symptom domain or side effect was less troublesome during clozapine treatment). In contrast, ratings<3 indicate that the variable was regarded as worse during clozapine treatment compared to treatment with the previous antipsychotic. Ratings equal to 3 indicate that the variable was not regarded as different during clozapine treatment compared to the previous antipsychotic treatment.

Table 4
Carers' views of clozapine's benefits and side effects compared to prior antipsychotic treatment (n = 33).

ITEM	Number of responses					Mean rating*
	Much worse [1] n (%%)	Worse [2] n (%)	No difference [3] n (%)	Better [4] n (%)	Much better [5] n (%)	
Hearing voices	0 (0 %)	0 (0 %)	9 (27.3 %)	8 (24.2 %)	16 (48.5 %)	**4.21**
Other unusual experiences	0 (0 %)	0 (0 %)	16 (48.5 %)	8 (24.2 %)	9 (27.3 %)	**3.79**
Paranoid thoughts	0 (0 %)	0 (0 %)	8 (24.2 %)	8 (24.2 %)	17 (51.5 %)	**4.27**
Thinking more clearly	0 (0 %)	0 (0 %)	3 (9.1 %)	17 (51.5 %)	13 (39.4 %)	**4.30**
Mood	0 (0 %)	0 (0 %)	4 (12.1 %)	14 (42.4 %)	15 (45.5 %)	**4.33**
Improving your quality of life	0 (0 %)	0 (0 %)	8 (24.2 %)	12 (36.4 %)	13 (39.4 %)	**4.15**
	0 (0 %)	0 (0 %)	11 (33.3 %)	12 (36.4 %)	10 (30.3 %)	**3.97**
Having more interest and being more active						
Excessive salivation	8 (24.2 %)	9 (27.3 %)	10 (30.3 %)	3 (9.1 %)	3 (9.1 %)	**2.52**
Weight gain	8 (24.2 %)	8 (24.2 %)	13 (39.4 %)	3 (9.1 %)	1 (3.0 %)	**2.42**
Daytime sedation	4 (12.1 %)	7 (21.2 %)	15 (45.5 %)	5 (15.2 %)	2 (6.1 %)	**2.82**
Overall side-effects	5 (15.2 %)	5 (15.2 %)	11 (33.3 %)	7 (21.2 %)	5 (15.2 %)	**3.06**

* Ratings greater than 3 indicate that the variable was regarded as better during clozapine treatment compared to treatment with the previous antipsychotic (i.e. a symptom domain or side effect was less troublesome during clozapine treatment). In contrast, ratings<3 indicate that the variable was regarded as worse during clozapine treatment compared to treatment with the previous antipsychotic. Ratings equal to 3 indicate that the variable was not regarded as different during clozapine treatment compared to the previous antipsychotic treatment.

HMC governance policies. Both patients and carers provided signed consent before taking part.

3. Results

3.1. Patient and carer characteristics (Table 1 and 2)

The study was conducted between January and December 2020. During this time a total of 100 patients in the HMC Psychiatry Department were prescribed clozapine, of whom 70 met the study entry criteria. All eligible patients were approached about the study and 42 of those eligible (60 %) agreed to take part and completed the assessment. Two thirds of the participating patients were male, and the most common diagnosis was schizophrenia (n = 37). Approximately half were Qatari. Most participants were single and living in the community. Thirty-three (79 %) had been prescribed clozapine for 5 years or more. With regard to concomitant psychotropic medications, 14 (33.3 %) patients were pre-

Table 5
Patients knowledge of interaction between smoking and clozapine treatment (n = 42).

Question	N (%)
What is your smoking status in terms of cigarettes?	
Not a current smoker	27 (64.3 %)
Smokes several times per week but no daily	0 (0 %)
Daily smoker < 10 cigs/day	6 (14.3 %)
Daily smoker greater than 10 cigs/day	9 (21.4 %)
What is your smoking status in terms of shisha?	
Don't smoke shisha at present	39 (92.9 %)
Smoke shisha occasionally i.e., at least once in the last month but less than once a week	3 (7.1 %)
Smoke shisha once a week	0 (0 %)
Smoke shisha 2 or 3 times per week	0 (0 %)
Smoke shisha most days	0 (0 %)
Are you aware that if you change the amount you smoke (cigarettes or shisha) it can affect the dose of clozapine that you need?	
Participant has good understanding including that stopping smoking can increase blood levels and lead to side effects	2 (4.8 %)
Participant has some awareness but vague and not sufficient for patient to know risks	6 (14.3 %)
Participant is not aware of relationship between smoking and Clozapine at all	34 (81.0 %)

scribed another antipsychotic (most commonly amisulpride), 14 (33.3 %) a mood stabilizer (most commonly valproate) and 12 (28.6 %) an antidepressant (most commonly fluoxetine). 20 participants were prescribed a medication for the management of either excessive salivation or extrapyramidal symptoms (glycopyrrolate = 12, benzhexol = 4, benztropine = 3, atropine = 1). Thirty-three carers participated with just over half being parents (Table 2). Male carers outnumbered female carers. The mean age of carers was 50 years. <10 % of carers lived with the patient.

3.2. Patients' views of clozapine's benefits and side effects compared to prior antipsychotic treatment (Table 3)

In terms of the mean ratings, patients rated clozapine as superior for all 7 potential benefits with this being most marked in terms of improving mood followed by reduction in 'hearing voices' and improving quality of life. In terms of 21 potential side effects, clozapine was rated as worse for all but 3 side effects ('stiffness', 'jerky movements of arms or legs', 'other abnormal movements e.g. shaking or tremor'). Of the side effects that were rated as worse with clozapine, the most marked differences were in terms of nocturnal salivation, weight gain, constipation, and increased appetite. Clozapine was rated as slightly better than the previous antipsychotic on the overall side effect rating item.

3.3. Carers' views of clozapine's benefits and side effects compared to prior antipsychotic treatment (Table 4)

Clozapine was rated as superior on all 7 potential benefits and in common with the views of patients the greatest benefit was in terms of improving mood. Carers rated Clozapine as worse than the prior antipsychotic in terms of excess salivation and weight gain but approximately the same as the previous antipsychotic in terms of overall side effects.

3.4. Patients knowledge of interaction between smoking and clozapine treatment (Table 5)

Patients' knowledge the potential interaction of clozapine with tobacco smoking was poor. This is despite nearly-one third of participants being smokers.

Table 6
Patients' views and knowledge on other aspects of clozapine treatment (n = 42).

Question	n (%)
Do you feel you received sufficient information about clozapine from HMC when you started it?	
Just the right amount of information received - it answered all my questions but did not overload me	14 (33.3 %)
I received some information, but more would have been better, most of my questions were answered but some remained	3 (7.1 %)
Inadequate information, I had many unanswered questions	25 (59.5 %)
Too much information, I felt overloaded	0 (0 %)
Did you receive any written information about clozapine or was it all verbal?	
Written information received (this was in addition to the standard manufacturer's leaflet in the pill box)	4 (9.5 %)
Only verbal information	18 (42.9 %)
No information received	20 (47.6 %)
Would you have like to have started clozapine earlier on during your illness?	
Yes	18 (42.9 %)
Unsure	19 (45.2 %)
No	5 (11.9 %)
Do you know why regular blood tests are needed when you take clozapine?	
Yes (correct answer required patient to refer to the need to measure the number of white blood cells)	19 (45.2 %)
No	23 (54.8 %)
Do you know what problems can occur if your white cell count becomes low?	
Yes (correct answer required the patient to refer to an infection that could be serious/fatal)	14 (33.3 %)
No	28 (66.7 %)
Do you know how often you need a blood test given that you are taking clozapine?	
Yes (correct answer required the patient to know how often her/she was required to have a full blood count*)	20 (47.6 %)
No	22 (52.4 %)
Do you currently see any other professional for your mental health other than your psychiatrist?	
Only psychiatrist	33 (78.6 %)
Yes, another mental health professional e.g., psychologist or nurse	9 (21.4 %)
Do you feel able to discuss your medication and side effects with your psychiatrist (and any other mental health professionals that you see, e.g., psychiatric nurse of pharmacist)?	
Fully	19 (45.2 %)
Partly	13 (31.0 %)
Only a little	6 (14.3 %)
Not at all	4 (9.5 %)
How likely are you to continue taking clozapine?	
I want to continue Clozapine long-term as I can see its benefits	15 (35.7 %)
I'll continue it as long as my doctor recommends it	18 (42.9 %)
I would like to stop it as soon as possible	9 (21.4 %)

* Weekly if prescribed clozapine for up to 18 weeks, 2 weekly if prescribed clozapine for between 18 and 52 weeks and 4 weekly if prescribed clozapine for more than 1 year.

3.5. Patients' views and knowledge on other aspects of clozapine treatment (Table 6)

Fourteen patients (33.3 %) reported that they had received the right amount of information about clozapine, 25 (59.5 %) described the information received as 'inadequate' and none felt that they had received an excessive amount of information about clozapine. Only 4 (9.5 %) had received written information on clozapine other than the standard manufacturer's information sheet and 20 (47.6 %) reported receiving no written information at all. Patients'

Table 7
Carers' views and knowledge on other aspects of clozapine treatment (n = 33).

Question	n (%)
Do you feel you received sufficient information about clozapine from HMC when you started it?	
Just the right amount of information received - it answered all my questions but did not overload me	15 (45.5 %)
I received some information, but more would have been better, most of my questions were answered but some remained	6 (18.2 %)
Inadequate information, I had many unanswered questions	12 (36.4 %)
Too much information, I felt overloaded	0 (0 %)
Did you receive any written information about clozapine or was it all verbal?	
Written information received (this was in addition to the standard manufacturer's leaflet in the pill box)	5 (15.2 %)
Only verbal information	19 (57.6 %)
No information received	9 (27.3 %)
Would you have like the patient you care for to have started clozapine earlier on during your illness?	
Yes	21 (63.6 %)
Unsure	11 (33.3 %)
No	1 (3.0 %)
Do you know why regular blood tests are needed when you take clozapine?	
Yes (correct answer required patient to refer to the need to measure the number of white blood cells)	26 (78.8 %)
No	7 (21.2 %)
Does carer know that a low WCC can lead to infection that can be serious/fatal?	
Yes (correct answer required the patient to refer to an infection that could be serious/fatal)	21 (63.6 %)
No	12 (36.4 %)
Do you know how often blood tests are needed when clozapine is prescribed?	
Yes (correct answer required the patient to know how often her/she was required to have a full blood count*)	25 (75.8 %)
No	8 (24.2 %)

* Weekly if prescribed clozapine for up to 18 weeks, 2 weekly if prescribed clozapine for between 18 and 52 weeks and 4 weekly if prescribed clozapine for more than 1 year.

knowledge about the need for hematological monitoring was poor. Most did not know that regular blood tests are needed to measure number of white blood cells and neutrophil count, that a low white cell count (WCC) can lead to infection that can be serious/fatal or the frequency with which they should have checks of their full blood count. Patient responses to the question 'How likely are you to continue taking clozapine?' were varied. Although 33 patients (79 %) wanted to continue clozapine long-term, as they could see the benefits or their doctor recommended it, 9 patients (21.4 %) stated that they wanted to stop it.

3.6. Carers' views and knowledge on other aspects of clozapine treatment (Table 7)

Less than half (45.5 %) of carers stated that they had received sufficient information on clozapine from the health service with over a quarter reporting that they had received no information at all. When information was received, it was generally verbal with only 15 % stating that they had received written information. Most (63.6 %) stated that they would have preferred that the patient that they cared for had started clozapine earlier in the illness history. A higher proportion of carers than patients answered correctly to each of the 3 questions on haematological monitoring. Despite this, a sizeable minority of carers lacked knowledge about the haematological monitoring needed during clozapine treatment. For example, 21 % of carers did not know that blood tests were conducted to measure the number of white blood cells, and 24 % did not know the recommended frequency of blood monitoring for the patient they cared for.

3.7. Correlation between patients and carers views on clozapine treatment

Generally, there were significantly positive correlation between patients and carers regarding the overall side effects of clozapine treatment, particularly with nocturnal salivation, weight gain, and sedation. Likewise, improvement in hearing voices paranoid thoughts correlated with improved quality of life.

4. Discussion

4.1. Strengths and limitations

As far as we are aware this is the first study to investigate the views of patients and carers to clozapine in the MENA region. It was conducted at the only dedicated psychiatric hospital in Qatar and the patient response rate was 60 %; both facts support the data being representative of patients with schizophrenia and related disorders who are prescribed clozapine in Qatar. Data for patients and carers was primarily gathered through interviews that were conducted by a research psychiatrist. In contrast, previous studies that have assessed patient views of clozapine have relied on patient completion questionnaires (Qurashi et al., 2015; Waserman and Criollo, 2000; Verma et al 2021). We opted to use a clinician administered interview to ensure that patients and carers fully understood the questions and that their views on clozapine were made in comparison to the antipsychotic prescribed prior to clozapine. In addition, the research team believed that an interview with an independent researcher, who could introduce the study and put the patient and carer at ease, was less likely to be associated with a social desirability bias in answers in comparison to a written questionnaire. The risk of social desirability bias was also reduced as the interviews with patients and carers were conducted by research psychiatrists who were not involved in clinical care of the participants.

The main limitation of the study is the small sample size. Only 100 patients were prescribed clozapine and only 70 patients met the entry criteria of whom 42 (60 %) agreed to participate with 33 associated carers also participating. The small sample size means the results should be regarded as provisional. Given the small number of patients prescribed clozapine in Qatar, a larger scale investigation of patient and carer attitudes to clozapine in the MENA region would best be achieved by conducting a study across several countries, ideally with similar cultural factors and similar design of psychiatric services. Another limitation is that several of the potential benefits of clozapine that were assessed are broad and cover a range of sub-items, but one cannot distinguish between these. For example, the biggest benefit of clozapine reported by patients in the study was improved mood. However the study cannot refine this further, for example to what extent improved mood indicates a reduction in depressed mood (Upthegrove et al., 2017), emotional blunting (Grigoriou & Upthegrove 2020) or anxiety (Temmingh & Stein 2015), symptoms that are all common in schizophrenia. This limitation could have been overcome be including more items in the structured interview but the team decided not to do this as a longer interview

could have reduced the response rate and the quality of the information gathered as a longer interview would make it more difficult for participants to concentrate throughout the interview.

4.2. Main findings

Overall, the results indicate that patients and carers regarded clozapine as superior to the previous antipsychotic treatment on 7 treatment items. Nearly half of patients and two thirds of carers indicated that they would have preferred clozapine to have been started earlier in the treatment history. Worldwide there are significant delays in starting clozapine treatment for people with TRS (John et al., 2018) with a UK finding an average delay of 4 years (Howes et al., 2012). Delays in starting clozapine treatment have been linked to poorer treatment outcomes (Varghese et al., 2020).

With regard to side effects, patients rated clozapine as worse than their prior antipsychotic treatment in terms of causing 18 of 21 side effects. The 3 side effects where clozapine was rated as less problematic that the prior antipsychotic were 'stiffness', 'jerky movements', and 'other abnormal movements'. This is consistent with data from a *meta*-analysis of randomized controlled trial that showed that clozapine has a low potential to cause extrapyramidal side effects (Huhn et al., 2019). The side effects that patients rated as most problematic with clozapine, compared to prior antipsychotic treatment, were nocturnal salivation, constipation and increased appetite. This is broadly consistent with previous studies of patients' views of clozapine treatment (Qurashi et al., 2015; Waserman and Criollo, 2000; Verma et al 2021). Although patients regarded most individual side effects as more problematic with clozapine compared to the prior antipsychotic, somewhat surprisingly they rated the overall burden of side effects as lower with clozapine that the prior antipsychotic. This suggests that extrapyramidal side effects, the only individual side effects rates as less problematic with clozapine, were particularly troublesome during prior treatment.

The potential impact of clozapine side effects can be mitigated in several ways. The first step is to monitor side effects to ensure that the clinician is aware of the problem faced by a patient. Several patient completion questionnaires can be used for this purpose including the Glasgow Antipsychotic Side-effects Scale for Clozapine (GASS-C) (Hynes et al, 2015). This contains 22 questions and requires only a few minutes to complete. It has recently been translated to Arabic (AlRuthia et al., 2018). Once side effects are identified, strategies can be implemented to reduce their impact. For example, several medications can help reduce excess salivation seen with clozapine (Sockalingam et al, 2007). In this sample nearly half of the participants were prescribed such medication. Behavioural strategies to manage weight gain associated with clozapine and other antipsychotics include diet and increased exercise (Dayabandara et al, 2017). In addition, metformin is a widely used off label option to reduce antipsychotic associated weight gain (de Silva et al., 2016).

Knowledge about the need for hematological monitoring and the potential interaction of clozapine with smoking were both poor among patients. Knowledge about haematological monitoring was better among carers but was still poor in at least a quarter. This is a concern as inadequate knowledge in both areas could lead to serious side effects and even death. The prevalence of agranulocytosis among clozapine-treated patients is 0.4 % (Li et al., 2020). Sudden cessation of smoking in patients prescribed clozapine can lead to increased serum clozapine levels and the appearance, or worsening, of side effects including somnolence, fatigue, hypersalivation, (Lowe and Ackman 2010), impaired consciousness (Ruissen et al., 2009) and seizures (McCarthy, 1994). The potential for this pharmacokinetic interaction is increased by the higher prevalence of smoking in people with serious mental illness (2–4 times higher) compared to the general population (Dickerson et al., 2018). The poor level of patient knowledge regarding the interaction between smoking and clozapine effectiveness may partly reflect smoking being allowed in certain areas on male psychiatric wards in Qatar (Badanapurkar et al., 2022). In turn this may lead to ward staff to assume that there is less priority to provide information to male inpatients about the pharmacokinetic interaction between smoking and clozapine.

The results show that greater efforts need to be made to provide information about clozapine and its side effects to patients considering, and prescribed, this drug and to their carers. We recommend that both verbal and written information on clozapine is provided to all patients and carers. Written information is important as patients and carers may have many areas that they wish to discuss with a clinician during a consultation making it difficult for them to retain all the verbal information that they are given. In addition, cognitive impairment, including problems with memory and attention, is common in people with schizophrenia and can contribute to difficulties in retaining information. Written information, in simple to understand language, can help overcome these problems as patients and carers can read it repeatedly. Involving a peer support worker, with experience of clozapine treatment, is another supplementary way to provide information about clozapine to patients who are considering starting this drug and to assist them make an informed choice about their management. Peer support workers can also assist in providing patients with information about many other aspects of management and self-care. However, it should be noted that currently there is only a small evidence base regarding the effectiveness of peer support workers in schizophrenia (Chien et al., 2019).

5. Conclusions

In conclusion, the study had three main findings. First, most patients with schizophrenia and related psychotic disorders who were prescribed clozapine in Qatar, as well as their carers, regarded clozapine as more effective in treating their illness than the previous antipsychotic that they had received. Most patients and carers expressed a wish that clozapine had been started earlier in the illness history. These findings support the wider and earlier use of clozapine in Qatar. There is no high-quality epidemiological data on the prevalence of schizophrenia in the general population in Qatar. Nevertheless, the fact there the population of Qatar is approximately 3 million and only 70 patients with schizophrenia and related disorders under the care of HMC were prescribed clozapine and met our inclusion criteria suggests that clozapine is underused to manage TRS in Qatar (Ismail et al., 2019) as it is in many other countries (John et al., 2018; Howes et al., 2012). The second major finding is that patients regarded side effects, other than extrapyramidal symptoms, as more problematic with clozapine compared to their prior antipsychotic. This highlights the need for clinicians to have expertise in managing clozapine side effects. Finally, the study shows that there is a need for psychiatric services in Qatar to provide higher quality information on clozapine to patients and their carers. We recommend that future research on patient and carer views on clozapine in the MENA region is conducted jointly across several countries to allow a larger and more representative data set to be compiled. This would also allow further analysis, for example whether views vary depending on the duration of illness prior to commencing clozapine.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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