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ORIGINAL RESEARCH

Investigating of the Experience of Subjective Well-Being of Clozapine Use in Patients with Treatment-Resistant Schizophrenia: A Mixed Method Study

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Background and Objective: While clozapine is an effective medication for treatment-resistant schizophrenia (TRS), adherence to treatment is often the focus of concern. The subjective experiences of patients with TRS treated with clozapine can be helpful in managing the concern related to its use. Therefore, this study aimed to explore the subjective well-being of patients with TRS treated with clozapine.

Materials and Methods: This study was conducted using a mixed-methods approach. In the quantitative part, data was gathered using two questionnaires, completed by 42 patients with TRS treated with clozapine. In the qualitative part, semi-structured interviews were conducted with seven patients to gather their experiences. The quantitative data were analyzed using descriptive statistics, and content analysis was used for analyzing qualitative data.

Results: Half of the participants in the quantitative part were female, and half were male. Their average age was 40.94 ± 10.89 years. The average duration of clozapine use among these patients was 71.66 ± 118.60 months. Study participants reported both positive and negative changes in their symptoms after clozapine use. The most substantial improvements were reported in mood (71.4% "better"), sleep (64.3% "better"), and quality of life (45.2% "much better"). Hypersalivation (21.4% "much worse"), abdominal pain (81% "worse"), and unusual sensations (64.3% "worse") were the most frequent negative experiences. The results of the qualitative analysis also showed that participants had subjective pleasant and unpleasant experiences. Pleasant experiences were related to symptom reduction and personal and family satisfaction with clozapine use, while unpleasant experiences were related to side effects and other issues with clozapine use.

Conclusion: The quantitative and qualitative results are strongly interconnected, revealing that subjective experiences of patients with TRS who used clozapine range from positive experiences, such as improved quality of life, to negative experiences, such as adverse side effects and contextual barriers. The results can be helpful for clinicians in the management of TRS patients treated with clozapine. Highlighting positive changes to patients and their families can increase adherence to treatment, and managing negative changes and adverse side effects can impact treatment outcomes.

Keywords: clozapine, treatment-resistant schizophrenia, subjective experiences, mixed method study

Introduction

Treatment-resistant schizophrenia (TRS) is a severe form of the disorder where patients do not respond to standard therapies. Compared to those in remission, individuals with TRS typically have a longer duration of illness, more pronounced negative symptoms, greater cognitive impairment, a higher suicide risk, and a poorer quality of life.[1] The diagnosis of TRS is based on specific criteria: (1) the presence of ongoing, moderately severe symptoms; (2) at least two adequate trials of different antipsychotic medications; (3) a treatment duration of six weeks or more at a dose equivalent to 600 mg of chlorpromazine daily; and (4) a documented medication adherence of at least 80%.[2]

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Clozapine is recognized as an effective treatment for TRS. This atypical antipsychotic has demonstrated superiority over other medications in reducing both positive and negative symptoms, improving overall functioning, and enhancing quality of life.[3] Despite its efficacy, the initiation of clozapine is often delayed, and physicians are frequently hesitant to prescribe it.

A qualitative study identified the primary barriers to clozapine prescription as being related to the drug itself, psychiatrists and the healthcare system, and patients and their families.[4] A nationwide survey investigating Iranian psychiatrists' attitudes toward clozapine use in patients with TRS reported that 40% of participants expressed concern about life-threatening side effects of clozapine, such as agranulocytosis and cardiomyopathy, which discouraged them from prescribing clozapine. 77% believed the risk of these side effects is still high. Also, 60% of them believed that identifying patients who would benefit from clozapine use is not easy. Planning strategies to reduce concerns about clozapine use was recommended in this study.[5]

There is growing emphasis on subjective well-being in schizophrenia treatment, reflecting a broader biopsychosocial approach. Patients' attitudes toward their treatment are now considered a key factor in evaluating outcomes.[6] Studies have examined the subjective well-being of patients on antipsychotics as both an important treatment outcome and a significant predictor of medication adherence.[7,8] However, research specifically on subjective well-being related to clozapine remains limited. Existing studies suggest that improvements in positive symptoms can predict better subjective well-being,[9] and enhancements in quality of life, social relationships, and self-awareness contribute to patient satisfaction.[10] Further research is needed to fully understand the impact of clozapine on subjective well-being and to promote its use in routine practice. Therefore, this study aimed to investigate the effects of clozapine on both symptom changes and subjective well-being in patients with TRS who had previously been treated with other antipsychotic medications.

Materials and Methods

Participants

Study participants were patients with TRS who were diagnosed by a psychiatrist and visited the psychiatry clinic at Farabi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran, from April 2021 to April 2022 (based on the Iranian calendar). The inclusion criteria for both quantitative and qualitative parts of study included a diagnosis of TRS (confirmed by a psychiatrist), at least three months of treatment with clozapine at a stable dose, and sufficient cognitive and behavioral capacity to participate in the study, as determined by the treating team. Patients receiving ECT or other antipsychotics concurrently, as well as those with substance use disorder, were excluded from the study. For the quantitative questionnaire, convenience sampling was used, and 42 eligible patients participated Table 1 presents participant demographic data.

For the qualitative part, purposeful sampling was used among those who participated in the quantitative part. Semi-structured interviews were used for data gathering.[11] The number of participants was determined based on the principle of saturation, ie, the point at which new data repeated previous findings and no longer provided fresh insights into the research questions.[12] Saturation was reached after seven interviews (four men and three women). Participants provided informed consent, with their capacity for consent determined by the treating team.

Study Design

The study was conducted using a mixed-methods design and employed a convergent approach. In this design, data collection and analysis of both qualitative and quantitative data occur simultaneously but are analyzed separately, aiming to create distinct yet complementary sets of data that inform one another.[13]

Quantitative Design

A cross - sectional descriptive study was considered. There is no standard questionnaire to assess clozapine treatment experience in the Iranian context. Therefore, we used the Clozapine Treatment Experiences Questionnaire, developed by Wasserman et al (2000),[8] which consists of 27 items assessing side effects of clozapine compared to previous

medications. Responses are recorded on a five-point Likert scale (much worse, worse, no different, better, and much better).[8] It should be remembered there is no previous report to test psychometric properties of the questionnaire. Before using this questionnaire, we translated it into Farsi, for this purpose, two independent researchers, both experts in English, translated it into Farsi. Then, at a joint meeting attended by an English language expert, a Farsi language expert, and two psychiatrists to rectify possible errors, the two versions were compared and merged into a single version. It was then back-translated into English by an expert in English. Discrepancies were resolved through a comparative review of the back-translated version and the original. Additionally, to ensure content validity, five psychiatrists reviewed the questionnaire and provided feedback, leading to the confirmation of the validity". Eligible patients (N=42) completed the questionnaire.

Qualitative Design

We used the conventional content analysis method for this part of the study. In this method, information is collected directly from participants, and codes, categories, and themes are developed from the provided text without imposing preexisting research theories.[14] Data was gathered through semi-structured interviews. The second author, who has significant experience in qualitative research, conducted all interviews. The interviews began with open-ended questions such as: "Please share your experiences with taking clozapine", "Please discuss any changes in your condition" and "Please describe any issues related to taking this medication". After their initial responses, more detailed questions were asked to explore the research topic further. Each interview lasted 20–30 minutes, and saturation was reached after the seventh interview.

Data Analysis

Quantitative Data Analysis

Descriptive statistical methods (mean and frequency) were applied using SPSS 25 software, with a significance level of 0.05. Due to the small sample size, further analytical analysis was not feasible.

Qualitative Data Analysis

Data analysis was conducted using the Graneheim and Lundman method through the following five steps.[15] First, all interviews were transcribed verbatim. Then, the interview texts were read line-by-line multiple times to gain a general understanding and familiarity with the content. In the third step, meaning units were identified and assigned initial codes. Then, the initial codes were discussed in weekly research team sessions. A constant comparison strategy was employed to distinguish categories from initial codes.[16] In the fifth step, the process continued until the subcategories emerged.

We used several strategies to ensure the study's rigor. Through constant comparison, extracted codes and concepts were continuously updated to reflect emerging themes and variations throughout the data collection process. A peer-check strategy was implemented to ensure the study's rigor. Peer checks were conducted weekly, allowing the research team to discuss emerging categories and subcategories. The personal interest of the researcher in the subject, reviewing the ideas of other researchers, and maintaining study documentation helped provide confirmability of the data.[17]

Ethical Considerations

This study received approval from the Ethics Committee of Kermanshah University of Medical Sciences (IR.KUMS.REC.1398.1018). Participants were assured of the confidentiality of their information, and written informed consent, including consent for the publication of anonymized responses and direct quotes, was obtained from all participants.

Results

Quantitative Results

Table 1 presents the demographic characteristics of the participants.

Table 1 Demographic Characteristics of Participants in Quantitative part of Study

Variable		Mean (SD)
Age (year)		40.94 (10.89)
Illness duration (month)		195.32 (91.51)
Clozapine use (month)		71.66±118.60
Gender (frequency (percent))	Male Female	21 (50) 21 (50)
Education (frequency (percent))	Illiterate Primary Secondary High school University	1(2.4) 5(11.9) 13 (31) 17 (40.5) 6 (14.3)
Marital status (frequency (percent))	Single Married Divorce	25 (59.5) 16 (38.1) 1 (2.4)

Notes: Values are expressed as mean ± SD unless otherwise stated.

As shown in Table 1, the participants' average age was 40.94 (10.89) years, with an equal distribution of males and females. The average duration of illness was 195.32 (91.51) months, and the average time on clozapine was 71.66 ± 118.60 months.

Table 2 presents changes in symptoms after initiating clozapine treatment compared to previous antipsychotic medications. As shown in Table 2, in the "much worse" category, nocturnal salivation (21.4%), weight gain (9.5%), and daytime salivation (9.5%) had the highest frequencies. In the "worse" category, abdominal pain (81%), unusual sensations (64.3%), and daytime hypersalivation (40.5%) were the most frequently reported symptoms.

Table 2 Subjective Experience of Side Effects Compared with Previous Antipsychotics

Symptoms Change	Much Worse Frequency (%)	Worse Frequency (%)	No Different Frequency (%)	Better Frequency (%)	Much Better Frequency (%)
Nocturnal salivation	9 (21.4)	17(40.5)	7 (16.7)	7 (16.7)	1(2.4)
Weight	4 (9.5)	9(21.4)	20(47.6)	6(14.3)	2(4.8)
Daytime salivation	4(9.5)	8(19)	21(50)	4 (9.5)	5(11.9)
Constipation	1(2.4)	9 (21.4)	26 (61.9)	5 (11.9)	0 (0)
Thirst	1(2.4)	5(11.9)	30 (71.4)	6 (14.3)	0(0)
Dry mouth	3(7.1)	3(7.1)	27(64.3)	7 (16.7)	2 (4.8)
Itchiness	0(0)	0(0)	30 (71.4)	10(23.8)	2 (4.8)
Unusual movements	0(0)	3 (7.1)	22 (52.4)	16(38.1)	1 (2.4)
Sweating	3(7.1)	4(9.5)	24(57.1)	9(21.4)	0(0)
Dizziness	2(4.8)	2(4.8)	29(69)	7 (16.7)	2 (4.8)
Wetting yourself – night	1 (2.4)	5 (11.9)	26 (61.9)	5 (11.9)	5 (11.9)
Vision	2 (4.8)	2 (4.8)	34 (81)	4(9.5)	2 (4.8)

(*Continued*)

Table 2 (Continued).

Symptoms Change	Much Worse Frequency (%)	Worse Frequency (%)	No Different Frequency (%)	Better Frequency (%)	Much Better Frequency (%)
Abdominal pain	0(0)	34 (81)	3(7.1)	2(4.8)	0(0)
Breathing	0(0)	3(7.1)	32(78)	7 (16.7)	0(0)
Energy levels	1 (2.4)	6 (14.3)	27 (64.3)	8 (19)	0(0)
Headache	2 (4.8)	3 (7.1)	29 (69)	6 (14.3)	0(0)
Unusual sensations	1(2.4)	27(64.3)	0 (0)	11 (26.2)	3 (7.1)
Urination	2(4.8)	4 (9.5)	27 (64.3)	6 (14.3)	2 (4.8)
Wetting yourself – day	0(0)	0(0)	33 (78.6)	5 (11.9)	2 (4.8)
Alertness	0(0)	6 (14.3)	16 (38.1)	16 (38.1)	3 (7.1)
Activity level	0(0)	3 (7.1)	10 (23.8)	20 (47.6)	8 (19)
Appetite	7 (16.7)	3 (7.1)	2 (4.8)	22 (52.4)	8 (19)
Sleep	2 (4.8)	1 (2.4)	2 (4.8)	27 (64.3)	9 (21.4)
Mood	0(0)	0(0)	6(14.3)	30 (71.4)	6 (14.3)
Thinking	1 (2.4)	0(0)	8 (19)	22 (52.4)	10 (23.8)
Social life	0(0)	0(0)	7(16.7)	17 (40.5)	18 (42.5)
Quality of life	0(0)	0(0)	11 (26.2)	12 (28.6)	19 (45.2)

In the "much better" category, the most frequently improved aspects were quality of life (45.2%), social relationships (42.5%), and thinking (23.8%). Additionally, improvements in mood (71.4%), sleep (64.3%), and both thinking and appetite (52.4%) were most frequently reported in the "better" category.

In the "no change" category, the most frequently unchanged aspects were vision (81%), daytime urinary incontinence (78.6%), and breathing (78%).

Qualitative Results

As previously mentioned, the qualitative part of the study involved interviews with seven participants—four men and three women. The average age of the participants was 43.85± (3.76) years. Table 3 shows demographic characteristics of the participants. Data analysis based on conventional content analysis resulted in the extraction of two main categories and five subcategories, as shown in Table 4.

Table 3 Demographic Characteristics of Participants in Qualitative Part of Study

Number	Age (Year)	Gender	Education	Marital Status	Illness Duration (Month)	Clozapine Use (Month)
1	44	Male	Secondary	Single	132	24
2	46	Male	High school	single	240	18
3	41	Male	High school	Single	180	72
4	48	Female	Secondary	Married	156	36

(*Continued*)

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Table 3 (Continued).

Number	Age (Year)	Gender	Education	Marital Status	Illness Duration (Month)	Clozapine Use (Month)
5	38	Female	Secondary	Married	240	20
6	42	Female	High school	Divorced	96	48
7	54	Male	Secondary	Married	132	24

Table 4 Extracted Category and Subcategory

Category	Subcategory	Code
Pleasant experiences	Illness management Reduction of illness symptoms Family satisfaction	Low need to hospitalization Anger reduction Better sleep Socialization Higher energy Peace in the family
Unpleasant experiences	Unpleasant side effects Associated problems Concern about life-threating effect.	Drooling Urination Sleepiness High cost of medication Lab test Heart attack Seizure

Pleasant Subjective Experiences

This category covers pleasant subjective experiences associated with satisfaction from taking clozapine, divided into three subcategories described below.

Illness management: Participants believed that clozapine helped control their illness. Before taking it, they required frequent hospitalizations, each time receiving different medications. One participant states:

> I am happy with this medicine because I no longer have to be hospitalized in a psychiatric hospital. I don't like being hospitalized. My illness is under control with this medicine. (participant 6, female, 42 years old)

Reduction of illness Symptoms: "Based on the study findings, taking clozapine has been associated with a reduction in both positive and negative symptoms, which patients have found satisfactory. One participant states:

> Since I started taking this medication, I feel much better. I used to get very angry and often disturbed my family, but now I'm much better. The medication has been very good for me. (Participant 1, male, 44 years old)

Another participants states:

> I feel I have improved a lot; I'm going to work now and sometimes going out with my family. I used to be very withdrawn and did nothing. (Participant 2, male, 46 years old)

Family Satisfaction: Participants reported that taking clozapine reduced their family's worries and increased their happiness, leading to an improved sense of well-being. One participant states:

> My mother constantly thanks God and prays for my psychiatrist. She says, 'We know how much better you have become, and they are happy about it. (Participant 4, female, 48 years old)

Unpleasant Subjective Experiences

The study findings indicate that taking clozapine is associated with unpleasant experiences and challenges for patients. This category has three subcategories, which we will describe.

Unpleasant Side Effects: Participants reported that clozapine has side effects that are difficult to tolerate, sometimes leading them to consider discontinuation. One participant states:

> When my psychiatrist told me this medication is very good, I was very happy, but this medication causes a lot of discomfort; I have constant drooling. My pillow is always wet. Some nights, like a child, I wet myself. (Participant 5, female, 38 years old)

Associated problems: Participants highlighted various challenges associated with taking clozapine, making continued use difficult. The need for frequent tests and the cost of the medication were among the issues mentioned. One participant states:

> Insurance does not cover the cost of the medication. I have to buy it out of pocket. Additionally, every time I go for a psychiatrist visit, I have to bring lab test results, which is hard. It costs money and requires time. Also someone needs to accompany me for these tasks. (Participant 7, male, 54 years old)

Concern About Life-Threating Effect

Participants expressed concerns about the life-threatening effects of clozapine. They reported that both they and their families were informed about clozapine's effects on body systems, which may lead to serious complications. One participant states:

> I searched the internet about clozapine. There are several negative effects, and I am concerned. I fear having a stroke, a seizure, and… (participant 3, male, 41 years old)

Discussion

This mixed-methods study provides an integrated perspective on the subjective well-being of Iranian patients with TRS undergoing clozapine therapy. The findings illustrate a complex interplay of significant benefits and considerable challenges, which are crucial for optimizing clinical management within the specific context of the Iranian healthcare system.The quantitative and qualitative results are strongly interconnected, revealing that the perceived efficacy of clozapine is a primary driver of subjective well-being. Quantitatively, the most substantial improvements were reported in mood (71.4% "better"), sleep (64.3% "better"), and quality of life (45.2% "much better"). These data are vividly contextualized by the qualitative findings, where participants described a transformative sense of illness control, reduced anger, improved socialization, and the ability to return to work. This aligns with the recent randomized controlled trial by Peraire et al (2025), which found that clozapine treatment led to significantly better subjective perception in patients with resistant schizophrenia and schizoaffective disorder.[18]

The importance of these positive changes is also significant from a clinical perspective. For example, insomnia has been linked to increased suicidality. McCall & Miller (2023) in their meta-analysis reported that Insomnia has been linked to increased suicidality (OR=1.84, 95% CI 1.28–2.65) and suicide attempt (OR=5.83, 95% CI 1.61–2.96) in patient with schizophrenia.[19] Conversely, another study reported that alleviating insomnia could reduce the risk of suicide following clozapine treatment.[20]

Furthermore, the reported stabilization of mood supports the findings of Peraire et al (2024), who identified clozapine's role as an effective mood stabilizer in schizoaffective disorder.[21] The convergence of data suggests that the positive impact on core symptoms and psychosocial functioning forms the foundation of patients' satisfaction, potentially leading to greater treatment adherence which is the focus of concern in these patients.

Finally, the patient's perception of family satisfaction with clozapine can impact on the quality of life of patients and care giver. The finding is align with the findings of Verma et al (2021).[22]

However, this positive experience is counterbalanced by a pronounced burden of adverse effects and systemic challenges. The quantitative data identified nocturnal hypersalivation (21.4% "much worse"), abdominal pain (81%

"worse"), and unusual sensations (64.3% "worse") as the most frequent negative experiences. The qualitative interviews provided depth to these statistics, with patients expressing significant distress over side effects like drooling, which impacted their daily lives and self-image. The finding is clinically important, because as reported in a systematic review by Grover and Naskar (2024), it can be a reason for discontinuation of clozapine by the patients which in turn has negative impact on outcome treatment.[23] Clinician should regularly assess these side effects and mange it. As discussed in a systematic review and qualitative analysis by Gurrera et al (2022) adverse side effect of clozapine including weigh gain, gastrointestinal hypomotility, clozapine-induced cardiomyopathy, and seizure usually emerge within three months and occur in the first 6 months after initiation. They also emphasized most of these side effects can be managed through dose reduction.[24]

Beyond the adverse side effects, the qualitative data uncovered critical systemic barriers unique to the patient's environment. Participants highlighted the financial strain of out-of-pocket medication costs and the logistical difficulty of obtaining mandatory frequent blood tests, concerns that were not captured by the quantitative scale. These findings must be interpreted within the cultural and economic context of Iran, where limitations in insurance coverage and access to healthcare services can disproportionately affect individuals with chronic conditions, potentially leading to non-adherence.[25] The finding is also reported in the results of a systematic review Baig et al (2021) who identified health care system barrier as a one of the main barriers to prescribe clozapine.[26] It seems that in addition to dedicated planning in the healthcare system, the cooperation of non-governmental organizations is essential to remove barriers to clozapine prescription.

Strengths and Limitations

As the first study of its kind on the subjective well-being of patients treated with clozapine in Iran, this research has notable strengths and limitations. This study employed a mixed-methods approach. In the quantitative component, patients reported the frequency of side effects and symptom changes after clozapine use compared to their previous medications. In the qualitative part, patients described their experiences with the drug, and the combination of these results provided rich information regarding clozapine use. The primary limitation of this study was the small sample size, which may affect its statistical power. It also prevented us to perform further analysis such as bivariate analysis. Secondly, we employed purposive sampling in the qualitative part of the study. This sampling method has inherent limitations, including selection bias, which may undermine the validity of the findings and restrict their generalizability.[27] Thirdly, although we included participants in the remission phase who had sufficient cognitive and behavioral capacity to participate, the impact of the illness on their ability to respond to questions should not be overlooked. A further limitation was the assessment of subjective well-being, as we only used a scale specifically related to clozapine. Using additional scales, such as the Subjective Well-Being Under Neuroleptics Scale, could have provided more comprehensive insights. Finally, this study focused on subjective experiences of changes and effects related to clozapine use but did not objectively assess these changes, such as their impact on quality of life using standardized questionnaires. Future studies should aim to address these limitations.

Conclusion

In line with the research objectives, this study generates the following key opinions. First, clozapine's value in the Iranian context is undeniable, primarily due to its superior efficacy in managing symptoms and improving quality of life where other treatments have failed. Second, the successful implementation of clozapine therapy requires a dual-focused approach: proactive management of physical side effects (eg, prophylactic measures for constipation, managing hyper-salivation) and systemic support to alleviate logistical and financial burdens. Clinicians must therefore engage in open dialogues about these challenges, validating patients' concerns and collaboratively developing management strategies. By acknowledging and addressing both the pharmacological and contextual obstacles, healthcare providers can better harness the significant benefits of clozapine, ultimately improving long-term outcomes for patients with TRS in Iran.

Data Sharing Statement

The datasets used and/or analyzed during this study are available in Persian. Due to confidentiality concerns, data can be accessed from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the research council and ethical committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (IR.KUMS.REC.1398.1018). Informed consent was obtained from all participants. The authors confirm that all methods were conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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