Refractory schizophrenia: quality of life and associated factors

Esquizofrenia refratária: qualidade de vida e fatores associados

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Abstract

Objective: To analyze the quality of life of people with refractory schizophrenia using clozapine, and its associated factors.

Methods: A cross-sectional study, conducted in the extended western region of Minas Gerais, which included patients with refractory schizophrenia using the antipsychotic, clozapine. For the measurement of quality of life, the Quality of Life Scale was used, specific for patients with schizophrenia. Univariate and multivariate analyses were performed.

Results: A total of 72 patients with a mean age of 42.9 years was part of the study. The overall score of the Quality of Life Scale indicated compromised quality of life, with a greater impairment in the social network domain (median = 2.36). The logistic regression analysis showed factors associated with a better quality of life. Conclusion: Low quality of life in patients with refractory schizophrenia was found. Physical activity, family income over three times the minimum wage, and having children were associated with a better quality of life.

Resumo

Objetivo: Analisar a qualidade de vida de pessoas com esquizofrenia refratária em uso de clozapina e seus fatores associados.

Métodos: Estudo de delineamento transversal, realizado na Região Ampliada Oeste de Minas Gerais, que incluiu pacientes com esquizofrenia refratária em uso do antipsicótico clozapina. Para a mensuração da qualidade de vida, foi utilizada a escala *Quality of Life Scale*, específica para pacientes com esquizofrenia. Foram realizadas análise univariada e multivariada.

Resultados: Participaram 72 pacientes, com média de idade de 42,9 anos. O escore global da *Quality of Life Scale* indicou qualidade de vida comprometida, com maior prejuízo no domínio rede social (mediana = 2,36). A análise de regressão logística apontou fatores associados a uma melhor qualidade de vida.

Conclusão: Evidenciou-se uma baixa qualidade de vida dos pacientes com esquizofrenia refratária. Praticar atividade física, renda familiar acima de três salários mínimos e possuir filhos foram associados à melhor qualidade de vida.

Introduction

Quality of life is related to subjective well-being and includes biological and psychological components, such as emotional well-being, awareness of one's own abilities and disabilities, possibility of adequate sleep and rest, vitality, and overall satisfaction with one's life.[1] It is a comprehensive and multifaceted concept, which also includes the complex relationship of the individual with society and his environment. In conditions of chronic diseases, including schizophrenia, the question of quality of life is more evident and complex, and is influenced by the length and severity of the disorder, the side effects of medications, as well as stressful events that interfere with the evolution of the problem. In addition, people who have schizophrenia are culturally stigmatized, which further compromises their social functioning.[2]

The importance of evaluating the quality of life in people with schizophrenia became more prominent in the last decade, as the recovery of patients also includes their reintegration in the family, workplace and social life.[3] In addition, efforts should not only be restricted to the transition to the community, but should also provide support for the maintenance of life.[4] Therefore, understanding the quality of life in schizophrenic individuals should refer to the full human experience: biological, psychosocial and environmental.

Paradoxically, the group of patients who have the most severe form of schizophrenia, known as refractory or resistant, is an uncommon focus of studies on quality of life and associated factors. Although there is not a single and globally accepted consensus, refractory schizophrenia can be characterized if there is no improvement in the main symptoms of the disease after treatment with two different classes of antipsychotics (at least one atypical), in suitable doses for a given period of time (four to six, or six to eight weeks).[5] Approximately 30% of the patients had the resistant form, and the treatment of choice is the use of the atypical antipsychotic, clozapine.[6]

Clozapine is considered a gold standard in the treatment of patients with refractory schizophrenia, and demonstrates a reduction in acute symptoms and the risk of suicide.[6] However, its use is not free of side effects, especially metabolic: weight gain, increased central adiposity, dyslipidemia, glucose intolerance, insulin resistance and high blood pressure, which characterize the metabolic syndrome.[7] Although these are the main and most common symptoms, there are also others associated with the use of clozapine, but without relevance to the metabolic syndrome.

Identifying factors that influence the quality of life in schizophrenia is therefore of fundamental importance, because it can help to define services and propose interventions to improve the life of these people.[8] In addition, antipsychotic medications, although representing a breakthrough in the treatment of this disorder, when they mitigate the negative symptoms, can trigger side effects or adverse reactions, which often influence the individual's functional capacity.[9] Thus, measuring the quality of life as a criterion of the treatment effect is especially important for patients who have refractory schizophrenia, considering that this disorder can cause an overall interference in many aspects of life.[3]

The analysis of the quality of life of people with refractory schizophrenia taking clozapine, with regard to the identification of associated factors, is scarce in the literature, especially in studies conducted in Brazil. Also, identifying and correlating clinical factors, such as the presence of metabolic syndrome, is of fundamental importance because this disorder is considered to be one of the main risk factors for cardiovascular disease in people with schizophrenia, and may be associated with a worsening quality of life.[10] Thus, this study is expected to fill part of this gap in the Brazilian literature on the subject, and provide information for the improvement of the practices of health professionals, particularly those from mental health and primary care.

Thus, the aim of this study was to analyze the quality of life of people with refractory schizophrenia taking clozapine, and its associated factors.

Methods

This was a cross-sectional analytical study, conducted at the extended western region of Minas Gerais,

with patients with refractory schizophrenia using the antipsychotic, clozapine. The inclusion criteria were: medical diagnosis of refractory schizophrenia; use of the atypical antipsychotic, clozapine; older than 18 years of age; both sexes; and capacity for understanding the questions. The exclusion criteria of the study were: pregnant women; participants who were not fasting; and those with any condition that might interfere with the data collection and measurement, for example, presence of any disability that would compromise the assessment of anthropometric characteristics. The need for fasting was related to the need for laboratory tests to identify the presence of metabolic syndrome.

The sample size calculation was performed using the OpenEpi program, version 3.03a, considering a population of 169 individuals for an expected event ratio of 50%, a significance level of 5%, and a 10% margin of error, estimating a sample of approximately 62 individuals. The final sample consisted of 72 participants.

The data collection period occurred during the months of December of 2014 to June of 2015. The patients with refractory schizophrenia in the extended western region of Minas Gerais were previously invited through letters and telephone contact, at which time they received all necessary information on the research. Data were collected at the Psychosocial Care Center Type III in the extended western region of, Minas Gerais, according to the date and time indicated.

The instrument used to measure and evaluate the quality of life of the participants was the *Quality of Life Scale*. It is considered one of the main specific instruments for measuring the quality of life in schizophrenic patients.[2] This scale was properly adapted and validated for use in the Brazilian context, receiving the QLS-BR acronym. Its dimensional structure has a total of 21 items, divided into three areas (social, occupational, and intrapsychic and interpersonal relationships), which include subjective and objective information relating to the functioning and symptoms of the patient in the three weeks preceding the interview. Scores of five and six reflect an unchanged quality of life; scores of two to four show a moderate involve-

ment; and scores of zero and one indicate a very impaired quality of life. It is also important to note that the blunted affect on quality of life was not assessed in this study, considering that this is the first study that specifically evaluated patients with refractory schizophrenia taking clozapine, as well as to avoid overlapping of the items of the *Quality of Life Scale* with other instruments that measure negative symptoms.

The categorization of the quality of life variable was based on the rating obtained by the scores, using the median value, and was divided into: unchanged, compromised, and very compromised quality of life. However, because of the almost insufficient amount of participants who presented with an unchanged quality of life, it was decided, for statistical reasons, to group the unchanged and compromised quality of life categories, which indicated better quality of life. The very compromised quality of life category was maintained.

For the collection of sociodemographic and clinical data, a semi-structured, pre-coded, and standardized questionnaire developed by the authors was used. For measuring the high-density lipoprotein cholesterol (HDL-C), triglyceride levels and glucose, which are criteria for metabolic syndrome classification, venous blood samples from the ulnar vein of the forearm were taken after 12 hours of fasting. The analysis was performed in the biochemical laboratory of the Federal University of Sao Joao del Rei / Midwest Campus Dona Lindu.

Metabolic syndrome was defined using the criteria of the *National Cholesterol Education Program* (NCEP) *Adult Treatment Panel III* (ATP-III) when of three or more of the following risk factors are present: abdominal obesity (waist circumference >102 cm in men or > 88 cm in women); high blood pressure (> 130/85 mmHg) or on antihypertensive treatment; hyperglycemia (fasting blood sugar > 100 mg/dL) or on hypoglycemic treatment; high concentration of triglycerides (> 150 mg/dL) or on medication to reduce this; low HDL-C (<40 mg/dL in men and <50 mg/dL in women), or on medication to treat low HDL-c.[11]

The processing and data analysis were performed using the Statistical Package for the Social Scienc-

es, version 20.0. To describe the results, tables for frequency distribution were used in the analysis of categorical variables and measures of central tendency, position and variability in the analysis of numerical variables. The chi square tests and Fisher's exact test were used in the analysis of categorical variables, and Mann-Whitney test, the analysis of numerical variables with asymmetric distribution, was used to evaluate the factors associated with the results of the QLS-BR scale in univariate analysis. For multivariate analysis, the binary logistic regression model was used. For input of the variables in the model, a p-value <0.20 in the univariate analysis was considered. The forward criterion was used and the 5% level of significance was adopted. The odds ratio (OR) was evaluated, adjusted with a respective 95% confidence interval (95%). The calibration of the model was assessed using the Hosmer-Lemeshow statistic.

The study was registered in Brazil under the Platform Presentation of Certificate number to Ethics Assessment (CAEE) 19436213.6.0000.5545.

Results

A total of 72 patients with refractory schizophrenia taking clozapine were evaluated, unintentionally found in both sexes in the same proportion (50%). The mean age was 42.9 years, and most were single (72.2%).

The overall score of the QLS-BR scale showed compromised quality of life. Regarding the distribution of scores on the scale, a greater commitment in the social network domain was found. The item affective-sex factor intrapsychic functions and interpersonal relationships presented a median <2, indicating severe impairment. There was no rating compatible with unchanged quality of life in any of the investigated items (Table 1).

Table 2 shows the relationship between the sociodemographic and clinical variables with the results of the global scale of the QLS-BR. Having children, family income above three times the minimum wage, and physical activities were associated with a better quality of life (p <0.05).

Table 1. Descriptive analysis of the results of the Brazilian version of the Quality of Life Scale (QLS-BR). Items, factors and global scale (n = 72)

Item	Factors	Mean±SD	Median*	Interquartile range	
				P25	P75
Interpersonal Relationships		2.5±1.2	2.36	1.71	3.25
1	Household		4.00	2.00	5.00
2	Friends		2.00	1.00	4.00
3	Acquaintances		2.00	0.25	2.00
4	Social activity		2.00	1.00	2.00
5	Social network		2.00	2.00	4.00
6	Social initiative		2.00	1.00	3.00
7	Withdrawal		2.00	2.00	4.00
Instrumental Role		3.1±1.4	3.00	2.20	4.15
9	Occupational role		2.00	1.00	2.75
10	Work functioning		2.00	0.00	2.75
11	Work level		2.00	0.00	4.00
12	Work satisfaction		4.00	4.00	9.00
17	Time use (aimless activity)		2.00	2.00	4.00
Intrapsychlc Foundations and Interpersonal Relationships		2.8±1.3	2.86	1.89	3.82
8	Socio-sexual relationship		1.00	0.00	2.00
13	Sense of purpose		2.00	1.00	4.00
15	Curiosity		2.00	1.00	3.75
18	Objects		4.00	3.00	6.00
19	Activities		4.00	2.00	4.00
20	Empathy		2.50	2.00	4.00
21	Emotional interaction		4.00	2.00	6.00
Common Objects & Activities		2.8±1.2	2.55	2.02	3.64
14	Motivation		2.00	1.00	3.00
16	Anhedonia		2.00	2.00	4.00

* Scores zero to 1.99 indicated very compromised quality of life; Scores 2 to 4.99 indicated compromised quality of life; Scores 5-6 indicate unchanged quality of life; SD - Standard Deviation

In contrast, other sociodemographic variables such as gender, age, marital status and employment status did not show significant association. In relation to clinical variables, none was associated with quality of life, nor with the presence of metabolic syndrome.

The results of the multivariate analysis of factors associated with a better quality of life are arranged in table 3. The family income (OR: 15.98), the practice of physical activity (OR: 25.24), and having children (OR: 24.92) have been associated (p <0.05) with a compromised or unchanged quality of life, or a better quality of life. The variable related to the frequency of psychiatric medical care was not included in the final model.

Table 2. Comparison of sociodemographic and clinical variables with the results of the Brazilian version of the Quality of Life Scale (QLS-BR) (n = 72)

Variables	Global Scale QLS-BR		p-value
	QL VC (n=15)	QL C/U (n=57)	
Sex			
Male	8	28	0.772*
Female	7	29	
Age			
Mean ± standard deviation	43.9±16.0	42.6± 9.1	0.735**
Median (Minimal – Maximal)	44 (30-52)	43 (22-59)	
Marital status			
Single	14	42	0.164***
With partner	1	15	
Educational level			
Elementary	10	30	0.227*
High school or above	4	26	
Children			
None	13	36	0.050*
Yes	1	21	
Are you currently working?			
Yes	0	7	0.332*
No	15	50	
Do you get retirement benefits?			
Yes	10	35	0.999***
No	4	17	
What is your current household income?			
Up to 2 times the MW	13	26	0.004*
3 times the MW or more	1	26	
Where do you receive psychiatric treatment?			
Public network	13	38	0.203***
Private network	2	19	
How long have you been receiving psychiatric treatment?*			
Up to 10 years	3	18	0.526***
More than 10 years	10	35	
How often do you go to the psychiatrist for consultation?			
At least once every six months	3	32	0.019*
Semiannually or annually	10	22	
Have you ever been hospitalized in a psychiatric hospital?			
Yes	12	44	0.999***
No	3	13	
How long have you used clozapine?			
Up to 5 years	6	13	0.180***
More than 5 years	7	38	
Hypertension			
No	12	46	0.999***
Yes	3	11	

to be continued

continuation

Variables	Global Scale QLS-BR		p-value
	QL VC (n=15)	QL C/U (n=57)	
Diabetes			
No	15	46	0.105***
Yes	0	11	
How many medicines do you take per day?			
Up to 3 medications	2	18	0.704***
4 or more	7	32	
Do you think the medication that you take affects you?			
No	10	37	0.313***
Yes	2	20	
Do you smoke?			
No	12	42	0.746***
Yes	3	15	
Do you currently consume alcohol?			
No	0	2	0.999***
Yes	15	54	
Do you practice any physical activity?			
No	11	32	0.044***
Yes	1	24	
Metabolic syndrome			0.529*
No	9	29	
Yes	6	28	

*Pearson's chi-square test; ** Mann-Whitney test; *** Fisher's exact test; QL - Quality of Life; MW - minimum wage; VC- Very Committed; C/U - Committed or Unchanged (considered better quality of life)

Table 3. Multivariate analysis (binary logistic regression) to evaluate the factors associated with a better quality of life (compromised or unchanged) according to the Brazilian version of the Quality of Life Scale (QLS-BR)

Factors	p-value*	OR	CI95% for OR	
			Lower limit	Upper limit
Household income				
Up to 2 times MW	-	1.00	-	-
3 times MW or higher	0.020	15.98	1.55	164.94
Physical activity				
No	-	1.00	-	-
Yes	0.006	25.24	2.48	257.12
Children				
No	-	1.00	-	-
Yes	0.007	24.92	2.43	255.48

*p-value Hosmer-Lemeshow test = 0.999; IC95% - Confidence interval- 95%; OR - Odds Ratio; MW - minimal wage

Discussion

The limitations of this study were related mainly to the cross-sectional design, which allows the establishment of a cause and effect relationship. For example, one cannot say that a better quality of life is a direct consequence of having children, or that it transcends it. Another important question referred to the need for caution when comparing the results of this study with others that have used different measurement instruments than the QLS-BR, considering that they are less close to the event. How-

ever, different perspectives to assess quality of life were used in this investigation, considering the lack of recent studies using this scale validated in Brazil. Thus, it is important to remember that generic measurement instruments are useful in comparing the population, while specific, such as the one used here, better evaluate the effects of schizophrenia treatment.[2] It is also important to note that, in this investigation, it was not possible to specifically assess negative symptoms such as affective blunting, nor the possible side effects related to clozapine and other psychotropics used, except those related to metabolic syndrome.

The results of this research have important implications for patient care with refractory schizophrenia patients taking clozapine. The change in the health care model with the consequent institutionalization of patients points to the need for community care, especially in the context of primary health care. In this regard, the assessment of quality of life is an important indicator for the establishment of care plans and policies related, particularly, to the group of critically ill patients, who are the most disadvantaged and stigmatized. Moreover, the results indicate factors that may be involved in a better quality of life in this group, which can be an important tool for planning actions based on the real needs of these people, with a focus on psychosocial rehabilitation.

The measurement of quality of life in people with schizophrenia reinforces an alarming result, considering that a significant portion of these studies indicate an impaired quality of life, to a lesser or greater degree.[12-14] This research shows that the assessment of quality of life showed compromise in all areas and items on the QLS-BR scale, which is corroborated by other studies.[15,16] However, it is remarkable that only one item (affective-sexual relationships), of 21 evaluated, showed marked impairment (very compromised quality of life), taking into consideration that this research involved critically ill patients. Probably the fact that the patients were stable, receiving outpatient treatment during the research influenced this finding. People presenting a refractory form of schizophrenia usually has some substantial impair related to affection and sometimes even in cognition, which does not mean that they are unable to understand what it is good for them, taking decisions according tho their relationship context.[17]

Regular physical activity, current family income, and having children were associated with better quality of life in the multivariate analysis. These findings may be related to the fact that the social domain presented the greatest loss, which indicates impasses on issues involving interpersonal relationships and other social problems derived, possibly, from their own mental framework. Thus, it is essential to promote stimulation and social support for these patients, with the support of the entire health care network.[18]

Physical activity showed a relationship with an improved quality of life (OR: 25.24). Regular exercise aimed at patients with schizophrenia can help to reduce body mass index, improve psychiatric symptoms, and lead to feelings of accomplishment and therefore provide an impact on quality of life.[19-21] In this sense, managers and professionals who work with this population should support the need for planning and implementation of initiatives to promote and encourage this practice in the routine of health services, including seeking of intersectoral partnerships.

Income was another variable that was associated with quality of life. The results indicate that family income above three times the minimum wage is a favorable indicator to the outcome in question (OR: 15.98). It is possible to infer that a reasonable minimum financial condition can provide more adequate living conditions through access to basic services, health and leisure facilities, increasing the feeling of well-being. The literature suggests that the financial condition is related directly to the quality of life in patients with schizophrenia, including the refractory form.[22,23] In view of this, it is important that these patients are referred to programs and strategies for income generation and psychosocial rehabilitation, a barrier that prevents access to a productive and independent life. It indicates their integration into workshops to generate employment and income or other social initiatives organized in a participatory manner. The customer needs to be attended along with his family, in an indispensable partnership with assistance from social services.

Having children was also an indicator that can influence the quality of life. Note that this variable is poorly documented in the literature. A study in Rio de Janeiro had the opposite result, since children were associated with lower quality of life.[16] In another study, this variable was not associated with quality of life.[24] It is believed that patients considered the most serious,

who had children, have stronger network support, and are more stimulated and receive more care, including follow-up treatment.

Other demographic factors such as age, sex, marital status and occupation, were not associated with quality of life in this study. Regarding sex, despite being controversial, women generally showed a higher level of quality of life.[7,25] Concerning the marital status, some studies indicate that being single is associated with worse quality of life, while married people show more satisfactory results.[23,24] However, occupational activity, which is important for the autonomy and development of interpersonal skills, appears to be associated with quality of life in some investigations.[14,16]

Regarding metabolic syndrome, the possibility of its association with quality of life was tested, and the result denied such questioning. The issue that surrounds this condition in the patient who has schizophrenia, especially in refractory form, is considered worrisome, as these changes can dramatically increase the risk of cardiovascular disease and diabetes mellitus type II.[26] A longitudinal study pointed to a high prevalence of metabolic syndrome in people who use clozapine.[6] Important and recent studies that assessed the relationship between this syndrome and the quality of life also did not show significant association, despite the high prevalence of metabolic syndrome and low quality of life of patients.[8,9,27] Thus, the planning and implementation of strategies to minimize the risk of metabolic disorders and therefore improve treatment adherence and quality of life, should be a major focus of individual treatment plans for these patients.

The use of three or more medications was present in 77.8% of patients with impaired quality of life, although without reaching statistical significance. It is difficult to establish a precise relationship between these variables, given that more severe patients generally use a higher number of medications, which may reflect poorer quality of life. It is also important to consider that the amount of medication used, according to some investigations, often relates to increased side effects and worse perceived health status, especially in those using clozapine.[28,29]

Conclusion

People with refractory schizophrenia taking clozapine have impaired quality of life in all areas and across all items of the Brazilian version of the *Quality of Life Scale* (QLS-BR). Physical activity, family income and having children were factors associated with a better quality of life. The presence of metabolic syndrome, although prevalent, was not related to quality of life. The evaluation of quality of life in these patients may help in the design of care and policies, as well as the measurement of treatment effects.

Collaborations

Pinto JAF, Nunes FDD and Souza ARS contributed in the project execution, data analysis and final editing. Freitas PHB collaborated with the design and implementation of design, analysis and interpretation of data, and review of the final content. Machado RM contributed with the project design, critical review and approval of the final version.

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