Cogitare Enfermagem

ORIGINAL ARTICLE

Carbamazepine: usage profile, associated medications, adverse events, and treatment adherence - a cross-sectional study*

HIGHLIGHTS

1. Most patients have low adherence to treatment.
2. Adverse events are associated with moderate to severe anxiety symptoms.
3. Most patients used carbamazepine for some type of mood disorder.
4. 60% of participants reported experiencing adverse events.

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ABSTRACT

Objective: To describe the profile, associated medications, potential adverse events (AE), anxiety levels, and treatment adherence among carbamazepine (CBZ) users. **Method:** Cross-sectional, descriptive, and analytical study conducted through a questionnaire and consultation of secondary data in medical records. The study was conducted in the public health system of the municipality of Ijuí. **Results:** 45.9% of participants used carbamazepine for some mood disorder and 35.3% for epilepsy. 60% of the population reported adverse events, and 20% believed these were associated with the use of carbamazepine. Drowsiness (40%) and dizziness (35.3%) were the most frequent adverse events. 51.8% of participants were considered polypharmacy users. Only 3.5% of respondents were considered fully adherent to treatment. **Conclusion:** It was possible to identify the profile of carbamazepine users, contributing to the understanding of the topic, given that there are few studies on this population in the literature.

DESCRIPTORS: Epilepsy; Patient Health Questionnaire; Prescription Drugs; Polypharmacy; Mood Disorders.

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INTRODUCTION

Carbamazepine (CBZ) is a tricyclic compound initially used to treat trigeminal neuralgia; it later became indicated for bipolar depression and epilepsy[1-2]. Despite the variety of options available, CBZ is among the five most widely consumed medications for epilepsy worldwide, due to its established use for decades[3]. In Brazil, it is an essential medication and is part of the National List of Medicines[4-5]. It is the first-line treatment for adults with focal epilepsy, along with phenytoin and valproic acid. In addition to being indicated by clinical protocols for schizophrenia, bipolar disorder, and mania, it can also be used, in conjunction with lithium, as a mood stabilizer for anxiety and depression[4].

The frequency of CBZ use varies according to the therapeutic indication. In a study with epilepsy patients in Kazakhstan, 64.3% of participants used it[6]. Among patients at the Psychosocial Care Center (CAPS) in the state of Minas Gerais, prescriptions for CBZ were 5.11%[7], and in the municipality of Ijuí (northwest of Rio Grande do Sul), it was 6.4%[8].

The mechanism of action of carbamazepine (CBZ) consists of blocking sodium channels in neurons and, consequently, inhibiting high-frequency repetitive neuronal activity[4]. Adverse events include dizziness, ataxia, mental and motor changes, hyponatremia, and arrhythmias[1-2]. The incidence of adverse events and adherence to treatment vary according to the population profile[9-10]. Therefore, it is extremely important to verify this data, as the level of adherence to medication is significantly associated with adverse effects[9,11].

Considering the particularities described above related to the use of CBZ, the objective of the study was to describe the profile, associated medications, any adverse events (AE), the level of anxiety, and the adherence of CBZ users.

METHOD

The study has an observational, cross-sectional, analytical, and quantitative design, aiming to describe the sociodemographic, clinical, and medication use profile of carbamazepine (CBZ) users in the public health system of Ijuí, Rio Grande do Sul. This work follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. The research was conducted with patients from the Psychosocial Care Center (CAPS) Colmeia and with users of the Primary Care Dispensing Pharmacy of the Unified Health System (SUS) in Ijuí, Rio Grande do Sul, Brazil. The data collection period was from January to July 2023.

Patients were identified through a) a report of carbamazepine (CBZ) dispensing in the computerized medication dispensing system of the municipality; b) access to the medical records of the CAPS and identification of CBZ use. Once identified, they were invited to participate in the study during their consultations at CAPS or when picking up CBZ at the SUS pharmacy in Ijuí. Another recruitment strategy was to schedule participation in the research, inviting individuals according to their availability to participate at CAPS, the Central Pharmacy, or at home.

From the reports, a population of 237 individuals was selected. After exclusions and losses, a sample of 85 participants was obtained (Figure 1). The inclusion criteria for the study were: having used carbamazepine (CBZ) for at least one week and being over 18 years of age at the time of data collection. Patients with a diagnosis of cancer or who were unable to answer the questionnaires were excluded.

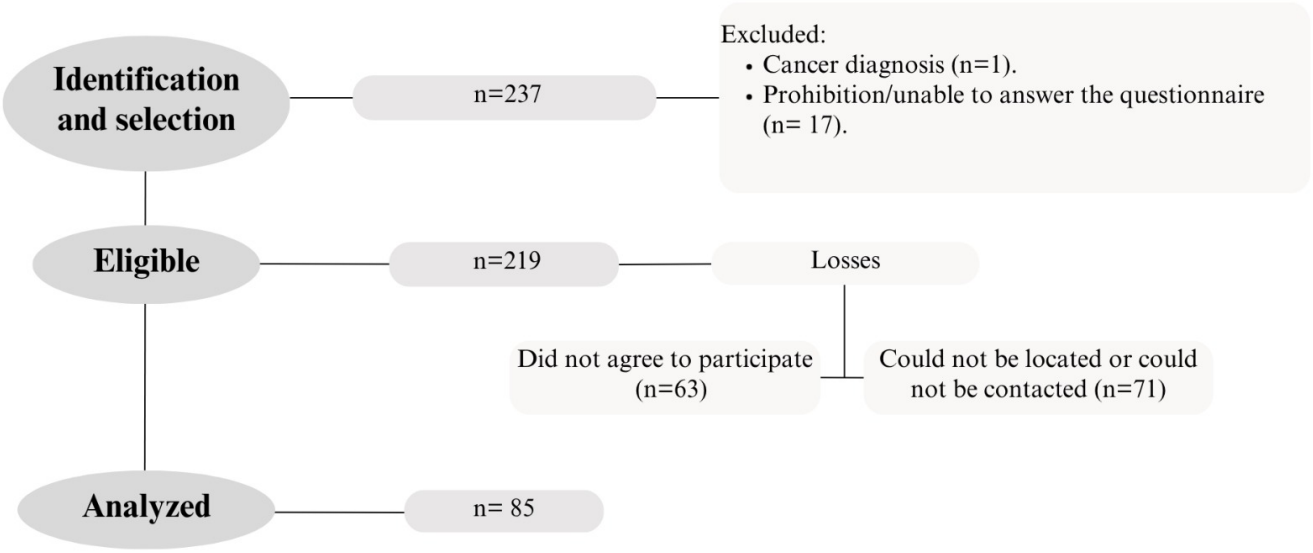

Figure 1. Flowchart for the selection and recruitment of participants. Ijuí, RS, Brazil, 2023

Source: The authors (2023).

Data were collected after the signing of the Informed Consent Form. A structured questionnaire was used. Data collection was conducted by the study proposer and a previously trained team. The medical records of the participants were also consulted to confirm the diagnosis and the medication administered.

Treatment adherence was assessed using the Brief Medication Questionnaire (BMQ), a previously validated instrument. The total score of the BMQ corresponds to the sum of its three domains: Regimen, Belief, and Recall. When the scores of the three domains are combined, the classification is defined as: adherent, including all patients with no positive responses in any domain; probable adherence, when the patient has a positive response in one domain; probable low adherence, when there are positive responses in two distinct domains; and low adherence, when all domains have a score ≥ 2[12].

The medications used were classified according to the Anatomical, Therapeutic, and Chemical Classification (ATC)[13]. The classification levels used were level 1 (main anatomical/pharmacological), level 2 (pharmacological or therapeutic), and level 5, referring to the medication itself. Adverse events (AEs) were self-reported by the participants, who first reported whether or not they had experienced these effects and then whether they believed these effects were related to carbamazepine (CBZ) or not.

The participants' anxiety was assessed using the Beck Anxiety Inventory (BAI), which identifies 21 anxiety symptoms observed in the previous week. Each symptom can be scored from 0 to 3, with 3 being the most severe. In the end, the total score can vary from 0 to 63 (the higher the score, the greater the anxiety). The overall score classification is: minimal anxiety (0-7), mild anxiety (8-15), moderate anxiety (16-25), and severe anxiety (26-63)[14].

The body mass index (BMI) was calculated by dividing the weight in kilograms (measured on a Multilaser© digital scale) by the square of the height (measured with a tape measure).

The study variables were: sex, age, education, BMI, medications used, diseases, AEs (according to the medication package insert), anxiety level, and degree of adherence.

This study was approved by the Research Ethics Committee of the Regional University of Northwestern State of Rio Grande do Sul, with opinion no. 5.840.304, dated December 27, 2022.

All analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 23.0.

The normality of the data was tested using the Kolmogorov-Smirnov test. Continuous data are presented as mean ± standard deviation (SD), and categorical data as absolute and relative frequency. The Pearson chi-square test was used to verify the association between two or more qualitative variables. A significance level of 5% was adopted for all tests.

RESULTS

Of the 85 participants, 47 were male (55.3%), 91.8% identified as white, 7.1% as mixed race, and 1.2% as black. The majority were married 39 (45.9%) and had incomplete elementary education 38 (44.7%) (Table 1). The average age was 49.00 ± 15.2 years, with a minimum of 20 and a maximum of 79 years. The average BMI was 29.5 ± 8.1.

Table 1. Marital status, education level, and BMI of carbamazepine users in the Unified Health System of the municipality of Ijuí (n=85). Ijuí, RS, Brazil, 2023

Variables	N	%
Marital Status		
Married	39	45.9
Single	35	41.2
Divorced	6	7.1
Widowed	5	5.9
Education Level		
Illiteracy	2	2.4
Incomplete Elementary Education	38	44.7
Complete Elementary Education	14	16.5
Incomplete High School	11	12.9
Complete High School	11	12.9
Higher Education	7	8.2
Postgraduate Education	2	2.4
Body Mass Index		
Low	3	3.5
Normal	21	24.7
Overweight	29	34.1
Obesity	21	24.7
Severe obesity	8	9.4
Not identified	3	3.5

Source: The authors (2023).

Regarding general diseases (self-reported), epilepsy was the most common, present in 37 cases (43.5%), followed by hypertension. Additionally, 14 participants (16.5%) stated they did not know the reason for using carbamazepine. The average duration

of use of this medication was 160.2 ± 127.5 months, with a minimum of 1 month and a maximum of 624 months. Most participants reported having experienced adverse events (AEs), with 51 cases (60.0%), and 17 (20.0%) believed that these events were associated with the use of carbamazepine. The most commonly mentioned effect by participants was drowsiness, with 34 cases (40%), followed by dizziness, with 30 cases (35.3%). The other data are presented in Table 2.

Table 2. Self-reported diseases and adverse events among carbamazepine users in the Unified Health System in the municipality of Ijuí (n=85). Ijuí, RS, Brazil, 2023

Variables	n	%
Diseases		
Epilepsia	37	43.5
Hypertension	26	30.6
Anxiety	25	29.4
Dyslipidemia	21	24.7
Depression	13	15.3
Diabetes	11	12.9
Hypothyroidism	8	9.4
Mood disorders	8	9.4
Gastritis/stomach problem	7	8.2
Bipolarity	5	5.9
Cardiopathy	4	4.7
Asthma	2	2.4
Anemia	2	2.4
Schizophrenia	2	2.4
Pulmonary emphysema	2	2.4
Rheumatoid arthritis	1	1.2
Migraine	1	1.2
Fibromyalgia	1	1.2
Labyrinthitis	1	1.2
Psoriasis	1	1.2
Rhinitis	1	1.2
General adverse events		
Drowsiness	34	40.0
Dizziness	30	35.3
Xerostomia	27	31.8
Headache	23	27.1
Abdominal pain	18	21.2
Irritability	16	18.8
Diplopia / blurred vision	16	18.8
Nausea/vomiting	13	15.3
Ataxia	10	11.8
Seizures	9	10.6
Respiratory depression/ dyspnea	7	8.2
Skin rash	4	4.7
Hypersensitivity reaction	2	2.4

Source: The authors (2023).

The majority of participants, 82 (96.5%), were using another medication in addition to carbamazepine continuously. The average number of medications was 5.2 ± 2.6, with fluoxetine being the most used, 24 (28.20%), followed by omeprazole and simvastatin, 18 (21.2%). In addition to the medications presented in Table 3, another 47 were reported by the participants. However, these were used by only 1.20% of the sample and are not included in the table. More than half of the participants were considered polypharmacy users, 43 (51.8%), for using 5 or more medications.

Table 3. Anatomical, therapeutic, and chemical classification of medications used by carbamazepine users in the health system of Ijuí (n=85). Ijuí, RS, Brazil, 2023

Level 1	Level 2	Level 5	N	%
A Dietary Treatment and Metabolism	A02 Medications for acid-related disorders	Pantoprazole	3	3.50
		Omeprazole	18	21.20
	A10 Medications used in diabetes	Insulin NPH	5	5.90
		Metformin	7	8.20
B Blood and Blood-Forming Organs	B01 Antithrombotic Agents	Acetylsalicylic acid	7	8.20
	B03 Antianemic Preparations	Vitamin B12	3	3.50
C Cardiovascular System	C03 Diuretics	Spironolactone	4	4.70
		Furosemide	4	4.70
		Hydrochlorothiazide	7	8.20
	C07 Beta Blockers	Metoprolol	4	4.7
	C09 Agents acting on the renin-angiotensin system	Enalapril	11	12.9
		Losartan	10	11.8
	C10 Lipid Modifying Agents	Simvastatin	18	21.2
H Systemic Hormonal Preparations	H03 Thyroid Therapy	Levothyroxine	10	11.80
N Nervous System	N03 Antiepileptics	Valproic acid	11	12.90
		Clonazepam	16	18.80
		Phenytoin	10	11.80
		Phenobarbital	15	17.60
		Lamotrigine	2	2.40
		Levetiracetam	3	3.50
		Topiramate	4	4.70
	N04 Antiparkinson medications	Biperiden	9	10.60
	N05 Psycholeptics	Chlorpromazine	16	18.80
		Clobazam	5	5.90
		Diazepam	12	14.10
		Haloperidol	4	4.70
		Olanzapine	3	3.50
		Risperidone	17	20.00
		Zolpidem	4	4.70
	N06 Psychoanaleptics	Amitriptyline	14	16.50
		Citalopram	5	5.90
		Clomipramine	1	1.20
		Fluoxetine	24	28.20
		Nortriptyline	5	5.90
		Sertraline	5	5.90

Source: The authors (2023).

According to the Beck Anxiety Inventory, the average score obtained was 14.02 ± 11.8, with a minimum of 0, a maximum of 50, and a median of 11. When classifying patients using the Beck Anxiety Inventory, the majority of participants, 34 (40.0%), exhibited minimal anxiety, and 13 (15.3%) showed severe anxiety symptoms (Table 4). Regarding treatment adherence, 38 participants (44.7%) demonstrated likely low adherence, while only three (3.5%) were adherent. As for the confirmed medical diagnosis in the records, most participants had some mood disorder (Table 4).

Table 4. Diagnosis according to the ICD-10 described in the medical records, level of treatment adherence, and anxiety among carbamazepine users in the Unified Health System (SUS) of the municipality of Ijuí (n=85). Ijuí, Rio Grande do Sul, Brazil, 2023

Variable	N	%
Diagnosis according to ICD		
Bipolarity	4	4.7
Mood disorder / mental disorder	9	10.6
Mood disorder, anxiety, and depression	1	1.2
Mood disorder and schizophrenia	1	1.2
Anxiety	7	8.2
Anxiety and depression	1	1.2
Depression	11	12.9
Depression and schizophrenia	1	1.2
Schizophrenia	4	4.7
Epilepsy / other seizures	30	35.3
Chronic pain	3	3.5
Not identified	13	15.3
Level of anxiety		
Minimum level of anxiety	34	40.0
Mild anxiety	20	23.5
Moderate anxiety	18	21.2
Severe anxiety	13	15.3
Treatment adherence level		
Adherent	3	3.5
Probable adherence	25	29.4
Probable low adherence	38	44.7
Low adherence	19	22.0

Source: The authors (2023).

Regarding anxiety symptoms, patients were divided into two groups: patients with low anxiety, 54 (63.5%) and patients with moderate/high anxiety, 31 (36.5%). The occurrence of adverse events (AEs) related to medication use (not necessarily carbamazepine) was assessed in these groups. Among patients with low anxiety, 29 (34.1%) reported no AEs, while among patients with moderate/high anxiety, only 5 (5.9%) reported no AEs. Thus, a significant association was observed between lower frequency of AEs and low anxiety (p=0.001). Additionally, when stratifying the population by therapeutic indication, the frequency of moderate/high anxiety was higher in patients with mood disorders (19; 76%), while in those with epilepsy, it was 6 (24%) (p=0.030).

DISCUSSION

In the present study, greater use of anticonvulsants in the management of mood disorders was observed, indicating a distinct prescribing profile compared to other contexts. In a study conducted in Colombia, for example, epilepsy was the main indication for the use of these medications, followed by neuropathic pain (26.8%), affective disorders (14.2%), and migraine prophylaxis (12.3%)[15].

Although most participants showed low treatment adherence, other studies[16-17], with patients whose conditions indicate the use of CBZ, described participants with higher treatment adherence. In a survey of individuals with bipolar disorder, 51% reported low adherence, and non-adherent individuals were younger, had family conflicts, polypharmacy, lower functioning, greater severity of mood symptoms, and comorbidities[17].

Similar results were found in a study in the United States with patients with bipolar disorder, in which only 28% were considered adherent[18]. However, it is worth noting that the differences observed in the literature may be attributed to the different populations, the diseases included, the medications used, and the various adherence questionnaires employed. Factors affecting treatment adherence include difficulties in accessing medication, multimorbidities, polypharmacy, the degree of trust in healthcare professionals, beliefs, negative self-perception of health, functional disability, adverse drug reactions, lower education levels, and logistical barriers (access to medication, timely prescription renewal)[10,19-20]. Low adherence to pharmacological treatment impacts disease control, potentially leading to therapeutic failure, worsening of the condition, and an increase in adverse events[20].

Differences in the profile of adverse events were observed compared to studies involving epileptic patients, in which fatigue (30.4%), headache (22.5%), and difficulty concentrating (19.6%) were the most frequently reported symptoms[9]. However, the symptoms are consistent with the carbamazepine package insert, which describes ataxia, dizziness, drowsiness, vomiting, and nausea as very common adverse events[21]. No comparative studies were found that included patients with mood disorders and epilepsy in their populations, as is the case in this study. Although the adverse events analyzed are possibly due to carbamazepine, since they were attributed to it in previous studies, the concomitant use of other medications should be considered, a practice that occurred among the participants in this study.

Patients on polypharmacy, who represented half of the sample, may be more susceptible to adverse events (AE) and drug interactions[2,5]. Additionally, some medications used by the participants in this study may result in similar AEs, such as simvastatin, which can cause side effects like headache, abdominal pain, nausea, vomiting, and dizziness[2,5]. Regarding drug interactions, it is noteworthy that fluoxetine is an inhibitor of the CYP3A4 enzyme, which metabolizes carbamazepine, increasing plasma concentrations of carbamazepine and consequently its side effects when used concomitantly. Other medications reported in this population have the potential to interact with carbamazepine, such as valproic acid, quetiapine, amitriptyline, and omeprazole[2,5,21]. These data justify the occurrence of AEs attributed to both carbamazepine and the medications used concomitantly.

Regarding the anxiety state of the participants, 15.3% exhibited more severe symptoms. These results are similar to those of epileptics treated at a hospital center in Canada, which used two assessment questionnaires, where 12.3% showed positive results for anxiety symptoms (BAI ≥ 22) and 30.3% for GAD symptoms (GAD-7 > 7 - Generalized Anxiety Disorder-7)[22]. As in the present study, a survey conducted in Mexico

identified a correlation between AEs and the Hospital Anxiety and Depression Scale (HADS); however, this study evaluated various anticonvulsants and also indicates that the severity of side effects may be correlated with psychiatric disorders[23]. The low level of anxiety in part of the population may also be explained by the study's own results, as some users of CBZ use the medication for neurological conditions where anxiety is not a central symptom. This was observed in the statistical analysis, which demonstrated greater anxiety specifically in patients with mood disorders. It is important to highlight that more than one-third of the studied population exhibited moderate or high anxiety (36.2%).

Regarding self-reported diseases, the high prevalence of epilepsy is justified by the fact that it is one of the therapeutic indications for carbamazepine (CBZ)[24] and a criterion for inclusion in this study, while hypertension is due to the high prevalence of this disease among Brazilians[25]. It is worth noting that diseases not related to the prescription of CBZ were obtained solely through self-report. This occurred because local clinical records are incomplete, as patients in Brazil consult both public and private medical services, and there is no single database to access this information. This justifies obtaining some information through self-report, although the bias of this data collection method is known.

The presence of various diseases in the population may be related to the high frequency of polypharmacy. Among the most commonly used medications are fluoxetine, omeprazole, and simvastatin. In a study with CAPS users in a region of Minas Gerais, the most prescribed medications were haloperidol, clonazepam, biperiden, diazepam, and valproic acid, and CBZ was used by only 5.11% of CAPS users[7]. In Colombia, analgesics, antiulcer medications, antihistamines, and antidepressants were more frequent in a population with epilepsy[15]. Similar to the results of the present work, in the Brazilian Federal District, fluoxetine was one of the most dispensed psychotropics.in a public pharmacy of the SUS[26]. It is important to highlight that the studies used for comparison differ in terms of location and target audience, which may explain certain differences in the results. Furthermore, carbamazepine is part of the National List of Essential Medicines (RENAME) in Brazil and is an essential medication for primary health care. In the study city, it was available for free through the SUS, as it was listed in the Municipal List of Essential Medicines (REMUME)[4].

The higher frequency of fluoxetine use in the population can be explained by the fact that it is one of the medications available for free through the SUS in the study city. This may also be related to its therapeutic indication as an antidepressant, being a selective serotonin reuptake inhibitor (SSRI)[2,5]. According to medical records, 16.8% had a diagnosis of depression (isolated or associated), while 15.3% self-reported this condition in the questionnaire. Various other psychiatric disorders also show clinical response to the use of selective serotonin reuptake inhibitors, including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, and bipolar disorder[2,5].

The high frequency of simvastatin use could be related to the risk of developing dyslipidemia due to carbamazepine (CBZ) use[27]. In vitro results suggest that CBZ is associated with an increase in non-HDL cholesterol levels, caused by a reduction in the expression of CYP7A1 (cholesterol 7-hydroxylase), an enzyme that controls the cholesterol metabolism rate[28]. Additionally, according to animal studies, CBZ promotes changes in enzymatic activities and transcription levels of enzymes/genes related to lipid metabolism, positively regulating lipogenesis[29]. This use could, therefore, be justified by iatrogenesis or the dietary characteristics of this population, which requires further research.

Regarding sociodemographic data, the majority were male, similar to the study conducted in Turkey[30], while in Jordan, the prevalence was female[16]. The average age of participants in the study conducted in the Turkish hospital was 45 years [30], similar to that observed in the present study, which was 49 years. In contrast, the study conducted in the United States reported a lower average age of patients, at 35 years, but it is worth noting that this study included only patients with mood disorders[18].

Based on the data found in this study, such as polypharmacy and adverse events among carbamazepine users, along with low adherence, this information needs to be used to support the development of a differentiated and careful follow-up for these patients, in order to achieve better treatment outcomes and quality of life.

Limitations include the lack of information in medical records, including the absence of a diagnosis (ICD-10) for 15% of study participants, as well as the lack of data to identify the type of epilepsy. Few studies on the same population and the use of carbamazepine for mood disorders were found, which complicates comparisons; in addition to the self-reported data on how the diseases and adverse events were reported. However, a distinguishing feature of this study is that it sought to provide more information about carbamazepine users.

CONCLUSION

Among the main findings, a higher frequency of carbamazepine (CBZ) use for mood disorders was observed. Fluoxetine, omeprazole, and simvastatin were the most commonly used medications by the participants, followed by carbamazepine. Half of the population was identified as polypharmacy users, with only 3.5% adhering to treatment, and the frequency of self-reported adverse events (AEs) was high. The study's distinguishing feature was the inclusion of different diagnoses for the use of CBZ, which allowed for a deeper understanding of the profile of these patients in Brazil, given that there is little data about this population in the literature.

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