

Prescription of benzodiazepines for adults and older adults from a mental health clinic

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Abstract *The aim of this study was to compare benzodiazepine (bzd) prescriptions for adults and older adults regarding appropriate use indicator. It is a cross-sectional study for collecting data on patients treated at the City's Mental Health Clinic in Sorocaba/SP, between March and December 2013. Appropriate use indicators were used: appropriate drug, with adequate posology and period of use; as well as the use of a single bzd, as anxiolytic for less than 3 months in depression treatment with antidepressants, use for less than 2 months if associated to an antidepressant and no use of long-acting bzd in older adults. From the 330 participants, most were women, with a family history of mental disorders and bzd use, without monitoring of a psychologist and using other psychotropic and polypharmacy ($p>0.05$). The minority of prescriptions had indication for the use of bzd (37.5% for older adults and 32.4% for adults) ($p>0.05$). Only 5.8% of the prescriptions for older adults and 1.9 for adults were rational ($p>0.05$). The chronic use was observed in all adults and older adults with depressive and anxiety disorders ($p>0.05$). A minority of prescriptions for adults and older adults was appropriate.*

Key words *Benzodiazepine, Unified Health System, Drug prescription, Rational use of drugs*

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Introduction

Benzodiazepines constitute a group of psychotropic more commonly used in the clinical practice due to their four main actions: anxiolytic, hypnotic, anticonvulsive and muscle relaxant¹⁻³. Generally, they are indicated to anxiety disorders, insomnia and epilepsy². The use of anxiolytics and hypnotics has considerably increased in the last decade⁴. In developed countries, such as Australia, France and Spain, these drugs are the most prescribed ones, and among them, benzodiazepines are the most common^{4,5}. Around 20 million prescriptions are written every year in the United States and approximately 10% of the population report having used benzodiazepine as a hypnotic⁶.

In Brazil, a research made in 2001 in 107 cities, with population over 200 thousand inhabitants showed that benzodiazepines were the third most used substance by the 8,589 individual interviewed⁷. A population study with 1,606 participants in the town of Bambuí (Minas Gerais, Brazil) observed the frequency of the use of these drugs in approximately 22% of the individuals with average age of 69, with prevalence in the use of long-acting benzodiazepines and for longer than 12 months⁸.

The effectiveness of these drugs for treating insomnia and anxiety disorders for a short period of time is described in literature. However, its use for long periods is not recommended, especially for older adults, due to the risk of developing addiction and other adverse effects^{9,11}.

The prolonged use of benzodiazepines, even in low dosages, is a risk factor for the development of adverse effects^{12,13} which can be described as somnolence, vertigo, tiredness, mental confusion, headache, anxiety, lethargy, ataxia, postural hypotension, retrograde amnesia, accidents, tolerance, addiction^{10,11} and increase in the frequency of falls^{14,15}.

Besides the period of use, there is some concern about the type of benzodiazepine prescribed, the long-acting ones are not recommended for older adults^{10,16} because they take longer for the body to eliminate them and for being associated to alterations arising from the ageing process, they may become risk factors for adverse effects^{2,15}. Beers criteria, developed to help selecting potentially inappropriate drugs for older adults follows the same recommendation¹⁷.

In spite of evidence in literature, benzodiazepines are largely used and commonly used inappropriately^{9,11,13}. The abuse, insufficiency or inadequacy in drug use harms the users and contrib-

utes to increasing expenses of public resources as well as to irrationality in its use¹⁸.

Thus, knowing the pattern of use of these psychotropic drugs at the Mental Health Clinic in the city of Sorocaba (São Paulo, Brazil) may contribute to decision making process of prescribers and health professionals when choosing those drugs. The benzodiazepines prescribed during the period of study were alprazolam, bromazepam, clonazepam, diazepam, estazolam, lorazepam, midazolam and nitrazepam. The present study aims to compare the benzodiazepines' appropriate use indicators among adults and older adults.

Methods

Context outline

It is a cross-sectional study, conducted at the Mental Health Clinic in the city of Sorocaba, São Paulo state, Brazil. The clinic treats the average of 4,600 patients/month distributed in medical, psychiatric and psychological treatment, occupational therapy, nursing care and drug supply. Around 1,200 medical appointments are conducted monthly.

Study population

Patients using benzodiazepines who had a single doctor's appointment at the clinic.

Eligibility criteria

Patients (18 years old or older) using benzodiazepines. Patients excluded were the ones that refused to participate in the study, which did not know the data asked during the interview and the ones whose medical charts were incomplete.

Data collection

All patients scheduled for a doctor's appointment and using benzodiazepines were invited to participate in the study, each patient was interviewed only once during the period of the study. The interviews were conducted between Monday and Thursday (the days of the doctor's appointment) in five periods of the week, between March and November, 2013.

The sample was calculated considering the frequency of 50% of inappropriate prescriptions (this figure enables a greater variance degree corresponding to the minimum size accepted for

the sample to be representative of a base population), confidence interval of 95% and margin of error of 10%. For sample size adjustments, a finite population of 1,200 treatments/month and 10% rate of no answers were considered, thus the sample size of 320 individuals was obtained.

The use of benzodiazepines was previously verified in patients' medical charts for the patients that would have a doctor's appointment. In order to avoid a new interview with the patient, the number of the medical charts was previously checked.

Information about the diagnosis(es) of mental disorder(s); benzodiazepine(s) used; as well as dosage, frequency and routes of administration; and use of other psychotropic were collected in the medical charts. Other variables were collected during the interview.

Data analysis

For the description of adults' and older adults' profiles, information on social demographic variables were collected, such as gender, age, marital status, occupation, schooling, family history for mental disorders and use of benzodiazepines; and for the clinic, data on the number of benzodiazepines in use, individual or group follow-up with psychologist, use of other psychotropic and antidepressants, presence of comorbidities and chronic diseases, and number of drugs in use. Polypharmacy was considered as the use of three or more drugs by the patient¹¹. Chronic disease was defined as in need of continuous management and were divided into three categories: non-transmissible (cardiovascular diseases, cancer and diabetes), transmissible (HIV/AIDS) and incapacitating (amputations, blindness and articular problems)¹⁹.

In the comparison of older adults and adults regarding the appropriate use, benzodiazepine rational use indicators were used (*appropriate drug*: with indication for use, lack of contraindication and contraindicated or severe drug interactions; *adequate posology*: dose and frequency recommended according to age group; and *adequate period of use*: identified according to patient's clinical diagnosis²⁰ and also other indicators (use of a single benzodiazepine for a period shorter than three months as hypnotic, anxiolytic, no use of alcohol, no neurodegenerative disturbances, except in the treatment for epilepsy, when chronic use is recommended; use for treating depression with antidepressants; use for a period shorter than two months when associated to

antidepressants⁹; and no long-acting benzodiazepine in older adults¹⁰).

Indication, posology, period of treatment and lack of contraindication and contraindicated or severe drug interactions were verified according to the data contained in the drug information system for Anvisa (Brazilian Sanitary Surveillance Agency) and Drugdex System²¹. Mantley et al.⁹ recommendations were used when there was no information about the period of treatment. The interactions were characterized as severe (life-threatening, may or may not need medical intervention to prevent or minimize adverse effects) or contraindicated (which absolutely impede the continuation of the concomitant use of the drugs)²². The clinical diagnoses were classified according to the 10th Edition of the International Classification of Disease (ICD 10).

Statistical Analysis

Categorical variables were presented through absolute and relative frequency while the quantitative ones with normal distribution through average and standard deviation. All variables were stratified into two populations: older adults and adults. Proportions were compared by chi-squared or Fisher exact tests and averages by student's t-test. The level of significance was 5%. Excel (2010 version) and Bioestat (version 5.3, Mimirauá Institute) were used.

Ethical aspects

The study was approved by the Ethic and Research Committee from the University of Sorocaba (207,662). Patients received the necessary information regarding the study from the researchers and signed the Free and Clarified Consent Term.

Results

From the 369 eligible patients, 330 were included, 210 adults (63.8%) and 120 older adults (36.2%) (chi-squared, $p \leq 0.001$). All patients who were invited to participate in the research accepted the invitation, but the exclusion criteria were lack of information during the interview ($n = 30$) or incomplete medical chart ($n = 9$) (Figure 1).

Table 1 describes the variables that characterize adults and older adults. Most of them were women, married individuals, with a family history of mental disorders and using benzodi-

azepines, without monitoring of a psychologist, using other associated psychotropic (antidepressants were the highlights) and using polypharmacy ($p > 0.05$). Most older adults were retired or on sick leave from work and had up to three years of school ($p \leq 0.05$). Chronic disease was the most frequent one in this group ($p \leq 0.05$).

No statistical difference was observed between the adults and the older adults regarding the frequency of the prescribed benzodiazepines ($p > 0.05$), clonazepam and diazepam were the most prescribed drugs (Table 2). The average period of time that adults and older adults used benzodiazepines was 7.6 ± 6.9 years and 7.9 ± 7.3 years, respectively, $p > 0.05$.

From the 120 prescriptions for older adults, 45 (37.5%) had indication for use. In adults, this result was observed in 67 (32.4%) of the 210 prescriptions. A higher percentage of diagnoses with indication for use was observed for clonazepam in older adults ($p > 0.05$). No prescription of estazolam, midazolam and nitrazepam presents indication for use (Table 3).

Severe drug interactions were observed in 21 adults and seven older adults, mainly due to the association of clonazepam to phenobarbital in adults ($p \leq 0.05$) and diazepam to phenobarbital in both groups ($p > 0.05$), with consequent risk of respiratory failure (Table 4).

Most of the use with precaution occurred with clonazepam ($p > 0.05$), and its use for a

time period longer than one year requires monitoring of the liver function and blood cell count. Individuals suffering from depressive disorders should use alprazolam or diazepam with precautions due to the increased risk of mania and suicide, situations observed in both groups ($p > 0.05$) (Table 4).

No difference was found between adults and older adults regarding rational use of benzodiazepines indicators ($p > 0.05$). From the 120 prescriptions for older adults, in only 5.8% benzodiazepines were used for the correct period of time. In adults, only four prescriptions (1.9%) were rational. No prescriptions of alprazolam, diazepam and lorazepam were rational (Table 5).

No differences were found between the groups regarding the other criteria of appropriate use of benzodiazepines ($p > 0.05$). However, the period of time for the use of benzodiazepines in the treatment of depressive and anxiety disorders was superior to the one preconized for all individuals (Table 5).

Discussion

The present study verified a predominance of benzodiazepine prescription for the adults treated at the mental health clinic. The inappropriate use of these psychotropic was observed in adults as well as in older adults, and a minority of the prescriptions was rational and had the recommended period of time for the use of benzodiazepines

The profile of the population studied was mainly women, married individuals, with a family history of mental disorders and using benzodiazepines, using other psychotropic and polypharmacy, and without the monitoring of a psychologist. The prevalence of the use of psychotropic in women, benzodiazepine among them, was observed in several studies^{3,8,11,23-25}, insomnia and anxiety were the main reasons women use these drugs³.

Antidepressants were the most prescribed psychotropic associated to benzodiazepine. This trend was also observed by Souza et al.³, who found that around 90% of the individuals interviewed used other psychotropic associated to benzodiazepine, mainly antidepressants; and by Netto et al.²³, who identified over 40 distinct therapeutic schemes involving benzodiazepines and antidepressants.

The association of benzodiazepines and antidepressants was referred to as the most common

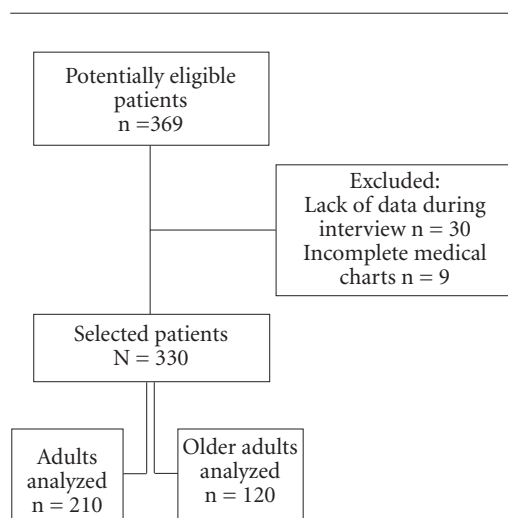


Figure 1. Flowchart of the selection of patients in the study.

Table 1. Sociodemographic and clinical characteristics of patients using benzodiazepines.

Variables	Adults n (%)	Older adults n (%)	p value
Gender			0.7053
Male	52 (24.8)	27 (22.5)	
Female	158 (75.2)	93 (77.5)	0.0001*
Age (years) average \pm sd	49.60 \pm 7.85	68.32 \pm 6.67	
Marital status			0.0001*
Single	42 (20)	10 (8.3)	
Married	127 (60.5)	66 (55.0)	
Widow(er) or divorced	41 (19.5)	44 (36.7)	
Occupation			0.0001*
Employed or domestic labor	100 (47.6)	15 (12.5)	
Unemployed	15 (7.2)	03 (2.5)	
Retired or sick leave	95 (45.2)	102 (85.0)	
Schooling			< 0.0001*
Illiterate	19 (9.0)	18 (15.0)	
From one to three years of school	88 (41.9)	74 (61.7)	
From four to seven years of school	39 (18.6)	18 (15.0)	
Eight or over eight years of school	64 (30.5)	10 (8.3)	
Family with mental disorders			0.0333*
No	60 (28.6)	48 (40.0)	
Yes	150 (71.4)	72 (60.0)	
Family member using bzd			0.3202
No	76 (36.2)	51 (42.5)	
Yes	134 (63.8)	69 (57.5)	
Monitoring of a psychologist			0.6726
No	190 (90.5)	111 (92.5)	
Yes	20 (9.5)	09 (7.5)	
Using other psychotropic			0.1569
No	16 (7.6)	15 (12.5)	
Yes	194 (92.4)	105 (87.5)	
Using antidepressants			0.8867
No	73 (34.8)	40 (33.3)	
Yes	137 (65.2)	80 (66.6)	
Comorbidities			0.0221*
1 a 3	167 (79.5)	106 (88.3)	
4 and over	43 (20.5)	14 (11.7)	
Chronic disease**			0.0012*
No	101 (48.1)	35 (29.2)	
Yes	109 (51.9)	85 (70.8)	
Number of drugs in use			0.9905
1 to 2	54 (25.7)	30 (25.0)	
Polypharmacy	156 (74.3)	90 (75.0)	
Total	210 (100)	120 (100)	

Sd = standard deviation. bzd – benzodiazepine. * Significant statistical difference (Student t test or chi-square, $p \leq 0.05$). ** The report of chronic diseases was according to referred author and includes arterial hypertension, diabetes mellitus, dyslipidemias, respiratory diseases, cardiovascular diseases and articular diseases.

one in the beginning of the treatment of depression, due to the presence of symptoms such as anxiety and insomnia²⁶. However, scientific evidence recommend the use of benzodiazepine as an adjuvant in treating depression only during

the first four weeks of the treatment, its prolonged use is not recommended due to adverse effects¹².

Anxiety Disorders Drug Treatment Guidelines²⁷ reports behavioral therapy as an effective

Table 2. Frequency of prescribed benzodiazepines.

Classification of benzodiazepines*	ATC	Adults n (%)	Older adults n (%)	p value
Long (40 to 250h)				
Diazepam	N05BA01	57 (26.2)	36 (29.2)	0.6384
Short to intermediary (12 to 40h)				
Alprazolam	N05BA12	36 (16.6)	20 (16.2)	0.9415
Bromazepam	N05BA08	5 (2.3)	7 (5.7)	0.1344
Clonazepam	N03AE01	113 (52.1)	54 (43.9)	0.1709
Estazolam	N05CD04	1 (0.5)	0 (0)	1.0000
Lorazepam	N05BA06	1 (0.5)	3 (2.4)	0.1427
Nitrazepam	N05CD02	4 (1.8)	2 (1.6)	1.0000
Short (1 to 12h)				
Midazolam	N05CD08	0 (0)	1 (0.8)	1.0000
Total**		217 (100)	123 (100)	

* According to half-life elimination³¹. ATC: Anatomical Therapeutic Chemical. No significant statistical difference (chi-squared or Fisher exact tests, $p > 0.05$). ** more than one benzodiazepine could be prescribed to a patient.

Table 3. Frequency of the number of patients with indication for use (n) regarding the number of patients who used benzodiazepines (N).

Benzodiazepines	n-adults (%) / N	n-older adults (%) / N	p value
Alprazolam	9 (25.0)/36	1 (5.2)/19	0.1385
Bromazepam	4 (80.0)/5	2 (28.6)/7	0.2424
Clonazepam	43 (38.4)/112	30 (57.7)/52	0.0088*
Diazepam	11 (21.2)/52	11 (27.0)/36	0.3298
Estazolam	0 (0)/1	-	-
Lorazepam	0 (0)/1	1 (20.0)/3	1.000
Midazolam	-	0 (0)/1	-
Nitrazepam	0 (0)/3	0 (0)/2	1.000
Total	67/210	45/120	

n = number of patients with indication for use. N = total number of patients who used benzodiazepines. (-) = no patient using benzodiazepines. * Significant statistical difference (chi-squared $p \leq 0.05$).

measure in patients suffering from anxiety disorders and recommends it as first line of treatment. However, it was observed that less than 10% of patients had behavioral therapy with a psychologist.

Chronic diseases were more frequent in older adults, a fact that may be justified by physiological changes related to the aging process¹⁵. It was observed in adults a more frequent presence of four or more comorbidities, indicating a higher number of psychiatric diseases per individuals in this group. Polypharmacy was frequent in adults and older adults, which corroborates with the results from the older adults studied by Noia et al.¹¹.

Clonazepam and diazepam were the most prescribed benzodiazepines in this study. This

result differed from the ones found in the studies by Noia et al.¹¹, Netto et al.²³ and Firmino et al.²⁴, which reported diazepam as the most prescribed benzodiazepine in health system for basic care from the Brazilian cities studied. Vicente Sanchez et al.⁵ found lorazepam; and Alvarenga et al.⁸ observed bromazepam and diazepam as the most used ones. It is important to note that these divergences may occur due to the different groups studied and/or the several drugs that are part of the list from these cities.

A minority of prescriptions had indication for benzodiazepine use in adults and older adults; bromazepam and clonazepam were the drugs more adequately prescribed for adults and, mainly clonazepam for older adults. Estazolam,

Table 4. Characterization of severe drug interactions and precaution in the use of benzodiazepines.

Description of severe drug interactions and precaution in the use of benzodiazepines		Adults n (%)	Older adults n (%)	p value
Severe interactions				
Interaction effects				
Alprazolam and fenobarbital	Decrease in the plasma levels of alprazolam	3 (1.4)	2 (1.6)	0.9940
Clonazepam and fenobarbital	Risk of respiratory depression (RD)	11 (5.2)	0 (0)	0.0087*
Diazepam and fenobarbital	Risk of RD	7 (3.3)	5 (4.1)	0.7632
Drug	Clinical condition	Justification for precaution in use		
Diazepam	Severe respiratory insufficiency	5 (2.4)	1 (0.8)	0.4225
Alprazolam	Depressive disorders	13 (6.2)	4 (3.3)	0.3101
	Chronic respiratory insufficiency	1 (0.47)	1 (0.8)	1
	Contraindicated for the age group	-	18 (15)	-
Clonazepam	Chronic respiratory disease	5 (2.4)	2 (1.6)	1
	Use for prolonged period of time	111 (52.8)	51 (42.5)	0.0899
Diazepam	Severe depression or associated to anxiety	12 (5.7)	5 (4.1)	0.8568
	Chronic respiratory insufficiency	5 (2.4)	2 (1.6)	1
Lorazepam	Contraindicated for the age group	-	3 (2.5)	-
Total		210 (100)	120 (100)	

*Significant statistical difference (Fisher exact tests, $p \leq 0.05$).**Table 5.** Frequency in appropriate use of benzodiazepines regarding rational drug use indicator and other appropriate use indicators.

Benzodiazepines appropriate use indicators	Adults n (%)	Older adults n (%)	p value
Drug rational use			
Correct indication	75 (35.7)	48 (40)	0.5117
Appropriate drug	64 (30.5)	45 (37.5)	0.2367
Correct dose	64 (30.5)	45 (37.5)	0.2367
Correct frequency	64 (30.5)	41 (34.2)	0.5690
Correct period of time*	4 (1.9)	7 (5.8)	0.1059
Total	210 (100)	120 (100)	
Other adequacy criteria			
Only one benzodiazepine per patient	204 (97.1)/210	117 (97.5) /120	1
Less than three months for anxiety disorders	0 (0) /57	0 (0) /25	-
Less than two months when associated to antidepressants	0 (0) /77	0 (0) /54	-
Use in treating depression with antidepressants	87 (88.8) /98	52 (85.2) /61	0.6240
No use of Long-acting benzodiazepines in older adults	-	84 (70) /120	-

*No significant statistical difference (chi-squared or Fisher exact tests, $p < 0.05$).

midazolam and nitrazepam were less prescribed and had no indication for use.

This could be justified by the fact that estazolam and nitrazepam are indicated for insomnia treatment²¹, and this diagnosis was not observed in the present study.

Alprazolam was prescribed for approximately 16% of the older adults of the study and only one prescription was appropriate. This drug should be used with precaution in this age group due to the risk of ataxia and oversedation, and the recommendation for dose adjustment was observed in only this prescription. Woelfel *et al.*²⁸ found that 20% used at least one potentially inappropriate drug, alprazolam the most common one. Similarly to alprazolam, three lorazepam prescriptions for older adults were inappropriate due to the risk of potentiating sedation²⁹.

Midazolam is preferably used as anxiolytic and sedative preoperatively due to its fast absorption, rapid onset and short elimination half-life². Therefore, its use is not recommended for clinical practices. In the present study, only one prescription for this drug was found.

It was observed that adults and older adults only used one benzodiazepine, which is adequate according to WHO recommendation³⁰. It was also observed that the majority of the depressed individuals used benzodiazepine associated to antidepressant, which is correct according to Mantley *et al.*⁹. However, the period of time using benzodiazepine for the treatment of depressive disorders (up to two months when associated to antidepressants) and anxiety (for a time period no longer than three months)⁹ was superior to the one preconized for all the individuals in the study, indicating a chronic use.

According to the Brazilian Psychiatric Guideline³¹, 50% of the individuals using benzodiazepine for over one year has an increased risk of abstinence syndrome, accidents, overdose (especially when associated to psychotropic), suicide attempt (especially in depressed individuals), reduction of the work capability and increase in the costs of hospitalization, exams and doctor's appointments.

Beers criteria¹⁷ suggest that benzodiazepines should be avoided by older adults and particularly the prolonged half-life ones, because they take longer to be eliminated from the body and are more susceptible to adverse effects³². Nevertheless, they are still commonly used in this population which can be justified according to Paquin *et al.*³³ due to the concern of the prescribers regarding a relapse of the older adults in the occasion of the drug discontinuation

In spite of that, the authors did not find any report of severe adverse effects in reducing the use of these drugs in older adults, thus this procedure is encouraged.

A study conducted in Quebec evaluated, similarly to the present study, some adequacy criteria in the use of benzodiazepines in older adults. The authors observed that approximately 50% of the patients received an inappropriate prescription, and that in around 20% of the older adults the prescription resulted in severe drug interactions³⁴.

According to Smith and Tett³⁵, clinical guidelines and restriction campaigns contribute to raise awareness of inappropriate use of benzodiazepines. However, in most countries, especially the developing countries, patients are not treated in the private sector as well as in the public sector according to clinical guidelines based on scientific evidence¹⁸, which would benefit the prescriber in the decision-making process.

The way data were collected, through interviews conducted in some periods of the week and according to the availability of the researchers or access to the clinic, may be considered as limitations in the present study. However, the number of participants in the study allowed data statistical analysis. It is important to mention that the loss in patients' number was small (around 10%) and the reason for it was either the lack of information given during the interviews or incomplete medical charts.

The study gathered some indicators described in scientific literature regarding the use of benzodiazepine aiming to delineate the use of this psychotropic in the City's Mental Health Clinic. Hopefully, the results observed may be useful for the improvement of the service provided by the professional involved in the care of patients using those drugs in the public health system.

Final Considerations

Comparing benzodiazepine appropriate use indicator between adults and older adults treated at the mental health clinic, their inappropriate use was observed in both groups and for the majority of the criteria assessed. A minority of prescriptions was rational or adequate regarding period of use, and the chronic use of benzodiazepine in patients with depressive and anxiety disorders was also observed.

The fact that the prescriptions were adequate for only 1.9% for adults and 5.8% of older adults draws the attention to error related to the indica-

tion for use, non-recommended procedures for the age group and/or patient; risk of severe drug interactions; and problems related to dose, frequency, and, mainly period of treatment.

Observing the findings in literature, it is possible to verify that part of the results found are similar to other Brazilian cities and even countries, demonstrating the need for initiatives for

planning interventions that aim the appropriate use of these drugs and that, consequently, benefit the patient. Incentives towards the improvement of professionals involved in the care of these patients and accuracy in the prescription of benzodiazepines could be some measures adopted aiming to provide the appropriate use of these psychotropic in this health service.

Contributors

DCC Naloto: experimental execution, data collection and writing; FC Lopes: experimental execution and data collection; S Barberato-Filho: construction of the methodology and final text design; LC Lopes: data interpretation and critical analysis; FS Del-Fiol: final correction and critical analysis; CC Bergamaschi: project conception, coordination, writing and final correction.

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