

Original Research Article

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DIAZEPAM INTERACTIONS WITH NEUROACTIVE DRUGS PRESCRIBED IN A BRAZILIAN PSYCHOSOCIAL CARE CENTER

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ABSTRACT: A study model encompassing: observational, descriptive, cross-sectional and retrospective parameters was undergone to evaluate the existence of drug interactions of Diazepam with other drugs that act in the CNS which are prescribed and dispensed in the Center of Psychosocial Attention (CAPS) of Mineiros (GO) Brazil. Henceforth, 3155 prescriptions and drug dispensations were analyzed from January to April 2017, using Micromedex® application to verify the possibility of interactions. It was found that 572 of the prescriptions contained the drug Diazepam, which corresponds to 18.13% of the total prescriptions. Regarding the possible polytherapies associated with Diazepam, it can be observed that this was prescribed frequently in the form of monotherapy presenting 352 prescriptions (61.54%) and 220 prescriptions (38.46%) with other drugs. The most frequent interactions were with amitriptyline (44.73%) and fluoxetine (39.37%), with mild to moderate severity. Therefore, it is necessary to know the interactions that occur frequently and the consequences of them so that these can be minimized or even avoided thus optimizing the pharmacotherapy of the users.

KEYWORDS: Diazepam; Mental health; Psychotropics; Drug interactions.

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1. INTRODUCTION

In 1842, Dom Pedro II Hospice was instituted in Rio de Janeiro - Brazil, wherein the employed therapeutic model was based in the hospitalization and isolation of those possessing mental illnesses [1-2-3]. The therapies therein used at the time were quite invasive and patients were frequently forced to perform agricultural work as a form of treatment. Nonetheless, the therapy was not humanized, and mostly resolved around violence [4-5-6]. Advances in medicine rose to prominence at the end of Brazilian colonial period, and their advent contributed to the emergence of new perspectives towards mental health treatments [1-2-7]. In this context, the Psychosocial Care Center Professor Luiz da Rocha Cerqueira was inaugurated in São Paulo in 1986 with the aim of replacing the hospital-centered model, avoiding admissions and favoring the exercise of civism and social inclusion of users and their families [1-4-8]. Concerning the treatment of mental illnesses, drugs that act on the central nervous system (CNS) are usually the first therapeutic alternative [9-10-11]. Despite being highly controlled substances, these drugs are used indiscriminately to increase the sensation of well-being, therefore configuring abuse [5-7-9]. Amongst CNS interfering drugs are benzodiazepines (BDZ), which came to prominence around the 60s and are considered the most prescribed drugs in the world [6-12-13]. In Brazil, data from Sanitary Surveillance show that, during 2007 to 2010, BDZ like drugs were listed among the most used in therapeutics [7-8-14]. In this context, poly-therapy has a major role in the treatment of mental disorders, and reports regarding drug interactions are noteworthy to improve patient safety. Henceforth, the present study is intended to analyze the existence of possible drug interactions between Diazepam and other drugs distributed by the mental health unit of Mineiros, Goiás, Brazil, in order to evaluate the clinical importance of these interactions.

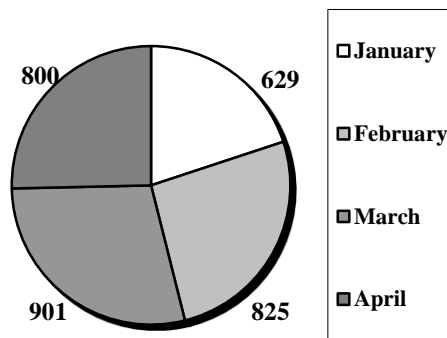
2. MATERIALS AND METHODS

This study was an observational, descriptive, cross-sectional and retrospective evaluation of the drug prescriptions dispensed at the center of psychosocial attention (CAPS) of Mineiros located in the state of Goiás, Brazil, with an estimated population of 61,623 inhabitants, its territorial unit area is of 9,060,091 Km² [15]. The work was approved under the number CAAE: 68494717.0.0000.5428 by the research ethics committee of Faculdades Integradas de Santa Fe do Sul - FISA / FUNEC according to resolution 466/12 that regulates research involving human beings. Although the work does not involve directly humans, and only evaluated data from medical prescriptions dispensed in CAPS. The research was performed through an analysis of the medical prescriptions delivered and dispensed in January, February, March and April of 2017, through a system based on cloud computing with the languages PHP 5.6 and JavaScript, wherein the databank was assessed and each revenue correlated to its user. Therefore, a total of 3155 dispensations were obtained in these months involving 2262 patients. Data collection was performed according to the data contained in the recipes (name of the drug, prescribed concentration, patient name, Brazilian health system (SUS)

number and date of dispensation). The classification of the prescribed psychotropics was performed according to the ATC system (Anatomical Therapeutic Chemical Classification System) [16]. Exclusion criteria were considered to be only totally illegible and / or undated recipes. The identification of prescribed drugs that act in the CNS along with Diazepam was made through the analysis of the total prescriptions and later separated according to the analyzed month. In order to analyze the interactions, Micromedex version 2.7.0[®] application was employed. All data was separated according to the severity of the interactions, namely: severe, moderate and mild.

3. RESULTS AND DISCUSSION

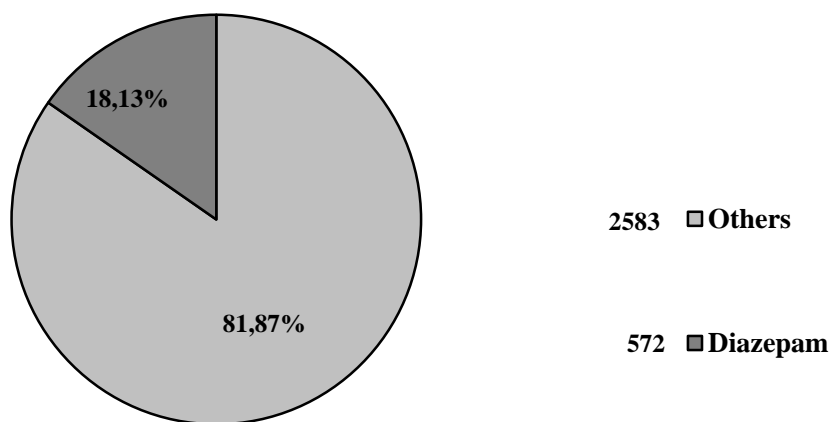
According to the analyzed data, a total of 3155 drugs were prescribed and dispensed in the months of January to April 2017. The amount of prescriptions dispensed and dispensed each month separately were: 629 in January, 825 in February, 901 in March and 800 in April, their representation in proportion is shown in figure 1, with an average of 788.75 prescriptions per month.



Source: research data.

Figure 1: Total revenues prescribed between January and April in the CAPS.

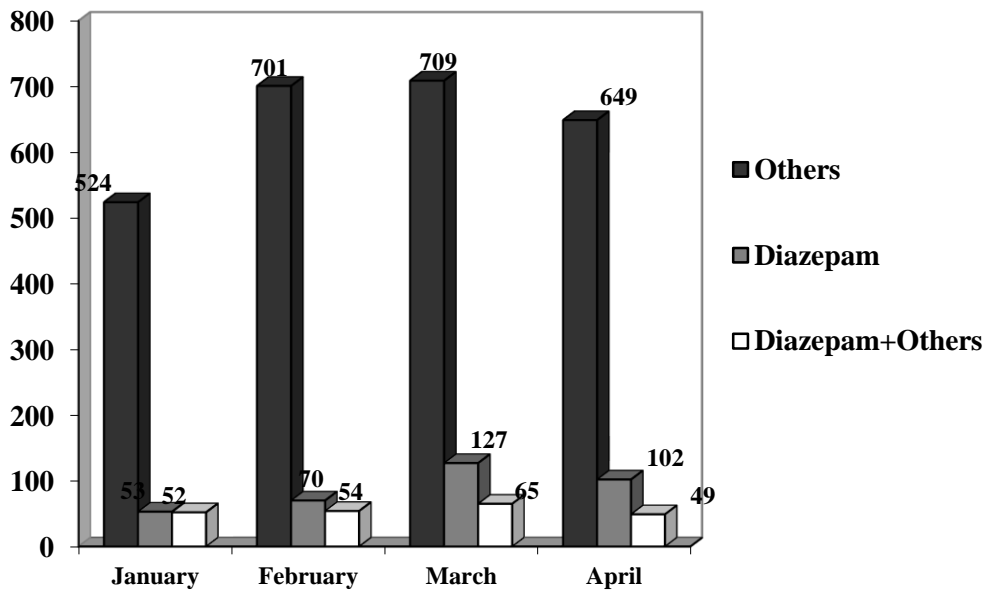
Of the 3155 prescribed drug products dispensed in the CAPS, those containing Diazepam were only 572, representing a total of 18.13% of the dispensations according to figure 2.



Source: research data.

Figure 2: Graphic representation of dispensations with Diazepam over other controlled drugs.

Analyzing each month, it is noticed that the month in which more dispensations of medicines of controlled use are made (without being the medicine Diazepam) was the month of March, with 709 recipes. Diazepam associations however, add up to a total of 65 dispensations, while only Diazepam was prescribed in 127 cases, as shown in figure 3. This may be correlated to the fact that the month of March had a greater number of dispensations, totaling 901 dispensations. One can analyze the amount of Diazepam prescriptions dispensed each month in both monotherapies and in polytherapies separately through the representation in figure 3 which shows that Diazepam was found to be mostly prescribed in monotherapies for all months.



Source: research data

Figure 3: Proportion of prescriptions correlating Diazepam and other controlled use medicines. Among the Diazepam associations prescribed are 220 in total, and 38 of these have interactions of clinical relevance according to Micromedex 2.7.0[®] application. Moreover, these were classified according to their severity as represented in table 1.

Table 1: Classification of drug interactions according to their severity.

Severity	Number of Drugs	Number of prescriptions	Percentage
Severe	3	6	15,80%
Moderate	1	17	44,73%
Light	1	15	39,37%
Total	5	38	100%

Source: research data.

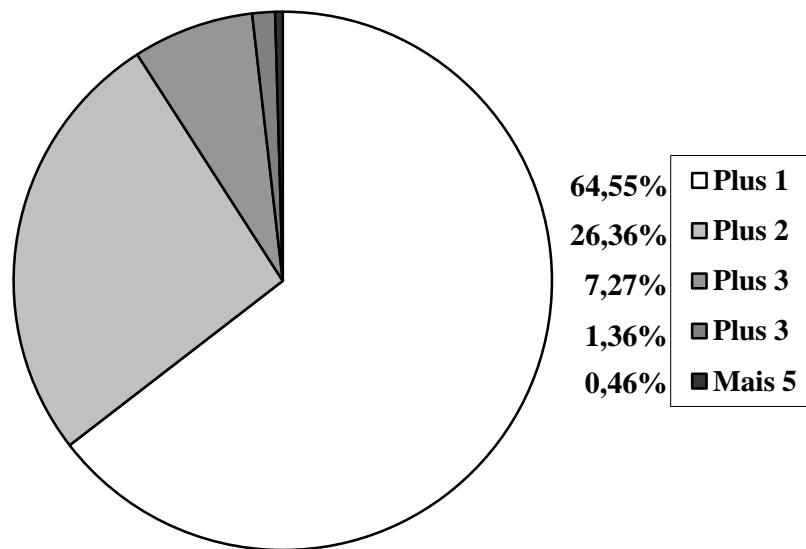
As observed in the table above, there are more serious interactions involving Diazepam than moderate and mild, but according to the data obtained in the research, the most prescribed drug with Diazepam was Amitriptyline, whose interaction is classified in moderate severity representing 44.73%. Table 2 shows the drugs that were prescribed and dispensed together with Diazepam (220 prescriptions) expressed in frequency (number of recipes found) and percentage that occurred within those four months (January-April).

Table 2: Prescriptions of Diazepam with other controlled use drugs.

Drugs	Frequency	Percentage
Valproic Acid	12	5,45%
Amitriptiline	17	7,73%
Biperiden	7	3,18%
Carbamazepin	46	20,91%
Lítium Carbonate	13	5,91%
Clomipramine	1	0,45%
Clonazepam	16	7,27%
Clorpromazine	10	4,55%
Phenitoin	1	0,45%
Phenobarbital	4	1,82%
Fluoxetin	15	6,82%
Haloperidol	18	8,18%
Nortriptilin	2	0,91%
Risperidone	42	19,1%
Sertraline	10	4,55%
Prometazine	5	2,27%
Olanzapine	1	0,45%
Total	220	100%

Source: research data.

The table above demonstrates all drugs that have been prescribed together with Diazepam, with emphasis on Carbamazepine and Respiridone with 20.91% and 19.1%, respectively, of the prescriptions, but these drugs are not of clinical importance in relation to the interactions with Diazepam. Through the search in the application database Micromedex 2.7.0[®] were found five drugs that interact with Diazepam, namely: Amitriptyline, Phenytoin, Phenobarbital, Fluoxetine and Olanzapine. Although there were other drugs prescribed together with Diazepam, those of clinical relevance were only five of 17 drugs representing 38 prescriptions and dispensations representing 17.27% over the other dispensations of other drugs prescribed together with Diazepam (220). The aim of the study was to investigate the amount of drugs prescribed capable of interacting with the CNS and also with Diazepam for the same patient as presented in Graph 4. Data analysis showed that 220 dispensations showed Diazepam associated with other drugs. It can be observed that the relationship of prescriptions involving Diazepam and one other drug represented 64.55% of the prescriptions already in association with two or more drugs 35.45%. The drugs that presented noteworthy interactions according to severity were: 1) phenobarbital (presenting elevated severity), phenytoin and olanzapine (which represent in the research 15.78%); 2) moderate interaction occurred with amitriptyline 44.73%; and mild was with fluoxetine 39.50% of a total of 38 drugs (100%). Table 3 shows the drugs that interact with the drug under study with the others as well as their complications in the human organism according to the application used.



Source: research data.

Figure 4: Number of drugs prescribed acting in the CNS together with Diazepam for the same patient

Table 3: Description of drugs that are involved in drug interactions with Diazepam as well as its complications, clinical management, severity and frequency

Drug	Interaction Effect	Clinical Management	Severity	Fr%
Amitriptyline	Psychomotor deficiency	Inform patient about adverse effect	Moderate	44,73%
Fenitoin	Decreased serum levels of phenytoin	Assess if administration is needed; perform dose adjustment.	Severe	2,63%
Phenobarbital	It results in additive respiratory depression	Monitoring due to respiratory depression; Adjustment in dose of one or both drugs may be necessary.	Severe	10,52%
Fluoxetine	May result in high serum concentrations with Diazepam	Monitor patients for signs and symptoms of excessive Diazepam concentrations; Dosage adjustment.	Light	39,50%
Olanzapine	Potential for excessive sedation and cardiorespiratory depression	Monitor patient; dose adjustment.	Severe	2,63%

Source: research data.

Fr%: Frequency in %

The drug classes that interact with Diazepam dispensed in the basic mental health unit were: Antidepressants (amitriptyline, fluoxetine), Antiepileptics (phenytoin), Anticonvulsant Barbiturates (phenobarbital), Antipsychotics (Olanzapine) according to the ATT / DD classification of the World Health Organization (1996) [3]. According to the aforementioned results, the drug interactions that occurred between Diazepam and the other drugs prescribed and dispensed at the CAPS are interactions of moderate and severe mild clinical relevance, with moderate interactions occurring more frequently within the analyzed. Previous works [17] concerning the dispensing of psychotropic drugs by the municipal public health system of Campo-Mourão, PR, Brazil showed that Diazepam obtained a percentage 59.7% of prescriptions a value higher than that found in prescriptions in CAPS de Mineiros. The data obtained showed that amitriptyline was the drug that presented a greater number of interactions with Diazepam, being this classification moderated according to previous reports [18] in a study of more frequent drug interactions between psychoactive drugs in a specialized mental health service performed in January to February of 2011, which showed furthermore that Diazepam and Amitriptyline were the most prescribed neuroactive drugs, representing 21% of the interactions, being this one the most frequent found in CAPS of Mineiros in the analyzed period representing 44,73% of the interactions with Diazepam. In addition to evaluating the interactions the research showed the use of Diazepam in relation to monotherapies

and polytherapias being this one more used in monotherapies. Other works [19] which underwent an evaluation of pharmacotherapeutic prescriptions in a CAPS of a municipality located in the southwest of Goiás, where it was shown that most prescriptions for the same patient involved more than one drug and that the monotherapy presented lower numbers representing 20.61%. Regarding the research on the interactions with Diazepam the data showed that this is more used in monotherapies representing 61.54% in relation to the polytherapies with 38.46%. In another study on the pharmacotherapeutic profile of adolescents using a CAPS for alcohol and drugs for children and adolescents in the state of Goiás, A previous work [20] verified that the drug Diazepam was one of the drugs that presented most possible drug interactions with 19.6%, a similar result found in the CAPS study in Mineiros where 17.27% of the interactions that occurred with Diazepam represented clinical importance, which highlights the importance and relevance of the research on drug interactions with Diazepam to know these interactions and their severity. Although the number of interactions has not been too large, it is noticed that in most of them it is necessary to monitor the patient and readjust doses. It shows the need to know the interactions that occur frequently and the consequences of them so that they can be minimized or even avoided thus optimizing the pharmacotherapy of the users. An evaluation of pharmacotherapy through a professional pharmacist with the doctor is indispensable so that together, they can find the best pharmacological treatment for the users individually, according to their need.

4. CONCLUSION

The research showed that in the CAPS of Mineiros, Goiás, there are drug interactions of Diazepam with other medicines that act in the CNS. It was found that about one quarter of the prescriptions contained the drug Diazepam, and monotherapies associated to Diazepam are more common than polytherapies. The most frequent interactions were with amitriptyline (44.73%) and fluoxetine (39.37%), with mild to moderate severity. Therefore, it is necessary to know the interactions that occur frequently and the consequences of them so that these can be minimized or even avoided thus optimizing the pharmacotherapy of the users and, henceforth, patient safety.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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