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ORIGINAL ARTICLE

Study on medication prescription in the elderly population: benzodiazepine use and potential drug interactions

Estudo do uso de medicamentos em idosos: uso de benzodiazepínicos e interações medicamentosas potenciais

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Abstract

Background: Prescription of medications for elderly individuals is complex, potentially involving polypharmacy, drug interactions, and inappropriate medication. Notable among the medications are benzodiazepines, whose long-term use is common and growing among the elderly population. **Objective:** This study aimed to evaluate the occurrence of potential drug interactions (PDI) in elderly community-dwelling patients who use benzodiazepines. **Method:** Cross-sectional study, conducted via household survey, with 73 elderly persons in Juiz de Fora, MG, Brazil. The search and classification of PDIs was carried out using the Micromedex® system. **Results:** The prevalence of benzodiazepine use in this population was 18.3% (95% CI, 15.2-21.6). The use of benzodiazepines was associated with polypharmacy ($p<0.01$; PR 3.03; 95% CI, 1.79-5.26). A total of 157 PDI occurrences were found in 69.9% of the elderly people assessed. Of these, 25 were related to benzodiazepines. In the elderly individuals who use benzodiazepines, polypharmacy was associated with PDI ($p<0.01$; PR = 16.13; 95% CI, 4.67-55.55). PDI occurrence was high in the elderly people who use benzodiazepines, including interactions of highly significant clinical value. **Conclusion:** In general, PDI is associated with polypharmacy, which demonstrates the need to rationalize drug use in the elderly population through continuous monitoring, seeking the simplest and safest possible therapeutic regimen.

Keywords: aging; drugs interactions; drug utilization.

Resumo

Introdução: A prescrição de medicamentos em idosos é complexa, envolvendo polifarmácia, interação medicamentosa e medicamentos inapropriados. Entre os medicamentos, destacam-se os benzodiazepínicos, cujo uso a longo prazo é comum e crescente entre idosos. **Objetivo:** Avaliar as interações medicamentosas potenciais (IMP) em idosos que usam benzodiazepínicos e vivem na comunidade. **Método:** Estudo transversal, realizado por meio de inquérito domiciliar, com 423 idosos de Juiz de Fora, Minas Gerais, Brasil. A busca e a classificação das IMP foram realizadas no Sistema Micromedex®. **Resultados:** A prevalência do uso de benzodiazepínicos na população foi de 18,3% (IC 95%: 15,2-21,6). O uso de benzodiazepínicos se mostrou associado à polifarmácia ($p < 0,01$; RP = 3,03; IC 95%: 1,79-5,26). Foram encontradas 157 ocorrências de IMP em 69,9% dos idosos, das quais 25 foram relacionadas aos benzodiazepínicos. Nos idosos que usavam benzodiazepínicos, a polifarmácia esteve associada às IMP ($p < 0,01$; RP = 16,13; IC 95%: 4,67-55,55). A ocorrência de IMP foi elevada nos idosos que usavam benzodiazepínicos, abrangendo interações de valor clínico altamente significativo. **Conclusão:** As interações detectadas podem apresentar ou induzir eventos adversos, comprometendo a segurança da farmacoterapia e demonstrando a importância de avaliar o processo de uso de medicamentos.

Palavras-chave: envelhecimento; interação de medicamentos, uso de medicamentos.

Study carried out in northern zone in the city of Juiz de Fora (MG), Brasil.
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INTRODUCTION

Brazil is undergoing an intense process of demographic and epidemiological transition characterized by an increase in the elderly population, changing the demographic and morbidity-mortality profiles of the population. Older people present well-known particularities: a larger number of chronic diseases, grater fragility, higher costs, and less social and financial resources. Regarding the aging process, it is becoming necessary to implement health policies with a focus on health promotion, disease prevention, and treatment that are specific for this age group[1].

Aging is accompanied by physiological and biochemical changes that can foster the development of diseases, many of them chronic, and predictors for drug therapy. Medications are a part of most treatment recommendations[2]. The increasing prevalence of chronic noncommunicable diseases in old age places the elderly population in the most medicalized age group of society[3].

The continued growth of drug consumption is also explained by the power of the pharmaceutical industry, drug marketing, and medicalization present in a significant portion of health professionals' training, as well as by the current health model, which considers medication as its main form of intervention[4].

Prescription of medications for the elderly population is extremely complex, involving drug interaction (DI) and inappropriate medication use. Although the prescription of multiple drugs can be sometimes clinically justified, it presents significant risks as it increases the probability of adverse drug-related events[5]. Considering the variables inherent in aging previously mentioned, the concomitant use of various medications requires a more careful approach and monitoring[6].

Due to the number of prescribed drugs, the complexity of treatment regimens, especially in the presence of comorbidities, and the pharmacokinetic and pharmacodynamic changes inherent in the aging process, older people are more vulnerable to adverse drug reactions, include DI[7].

Because the elderly population is constantly afflicted by insomnia and anxiety, psychotropic drugs, especially antidepressants and benzodiazepines, are among the medications chronically used by this group[8].

According to the Beers-Fick and Screening Tool of Older Persons' Prescriptions (STOPP) criteria, benzodiazepines are considered inappropriate for older people, and their use should be avoided in this population independent of the half-life of the drug prescribed[9,10]. Consumption of benzodiazepines is associated with many adverse effects, including sedation, amnesia, cognitive impairment and ataxia, with possible deterioration of attention[2,8].

Chronic use of benzodiazepines can have serious consequences, such as increased adverse effects, development of dependence, and tolerance[11,12]. Nevertheless, the long-term use of benzodiazepines by the elderly population is common and growing[2].

In this context, this study aims to assess the occurrence of potential drug interaction (PDI) in elderly community-dwelling persons who use benzodiazepines.

METHOD

The present study originates from an observational follow-up study conducted with elderly residents in the northern district of the municipality of Juiz de Fora, state of Minas Gerais, Brazil[13]. This is a cross-sectional study, part of the second cross-section phase. The sample is representative of the city's population, and the northern district is the largest territorial region in the urban area, the second largest in terms of population size, and aggregates the largest number of neighborhoods and greatest concentration of substandard settlements and social programs[13].

Data were obtained via two household surveys conducted in 2010 and 2014-2015. The present study is part of the second cross-section phase. The individuals were selected through cluster sampling, with the primary sampling subunits being census tracts. Since the actual survey had multiple outcomes, the sample size was calculated based on a prevalence of 50%, design effect (DEFF) of 1.5 (considering effect of stratification and cluster), and significance level of 95%[13].

All the elderly individuals who participated in the first survey were revisited. Losses over the course of years included change of address with impossibility to identify the new address, situations in which the elderly individuals were not reached after three attempts to contact them on different days and times, and refusal. To compensate for losses, the oversample method[14] was used, with cluster sampling. Thus, the study sample consisted of 423 elderly individuals: 248 participants of the 2010 study and, 175 additional individuals[13].

The questionnaire was standardized and pre-tested. Data collection was performed in the elderly persons' homes from September 2014 to March 2015. Quality control was conducted on the information collected, in which 10% of the sample were reassessed by another partial interview. The Mini-Mental State Examination was used to screen cognitive impairment[15]. Elderly persons who could not attain the minimum established for the study[16] had the questionnaire answered by a caregiver/family member. In the absence of another respondent, the elderly person was excluded from the study.

The following question was used to assess the use of medications: "Do you take any medication continuously?" In case of affirmative answer, the boxes or packaging of the drugs was verified. In their absence, the information was completed according to the elderly person's report. The study considered the use of five or more medications as polypharmacy[17].

The Anatomical Therapeutic Chemical (ATC) classification system, proposed by the World Health Organization (WHO), was used to classify the medications. The ATC system divides the active ingredients into different groups according to the organ or system in which they operate and their therapeutic, pharmacological and chemical properties. In this study, the medications were classified only into the main anatomical groups, i.e., the first level of the system[18].

Benzodiazepines were classified according to their elimination half-life[19]: short- / intermediate-acting (half-life ≤24 h), and long-acting (half-life >24 h)[20]. The duration of continuous treatment with benzodiazepines was stratified as follows: up to six months of treatment, or more than six months, with the latter considered as long term[19].

The study sample was composed of 73 elderly persons who use benzodiazepine. To assess the PDI, the study included elderly people who use two or more medications, one of them a benzodiazepine. The search and classification regarding the severity and documentation of PDI (drug-drug interaction) was performed based on the Micromedex® system[21], an online reference database of drug information, toxicology, diseases, acute care, and alternative medicine. Delivered through a website, this comprehensive resource provides healthcare professionals with clinical support for informed treatment decisions. The Micromedex® system facilitates decision-making in the areas of drug information, disease and condition management, toxicology, and alternative medicine[21].

The PDIs found were also classified according to their clinical value (Table 1), which relates to the severity and documentation of the interactions, using the following recommendations: (1) avoid combinations; (2) usually avoid combinations; (3) minimize risk; (4) no action is required; (5) there is no interaction[23]. Those meeting the conditions of clinical value 1 or 2 were considered as highly significant PDI[23].

Table 1. Classification of the clinical value of Potential Drug Interactions

Severity	Documentation			
	Excellent	Good	Fair	Unknown
Contraindicated	1	1	1	5
Important	1	1	1	5
Moderate	2	2	2	5
Secondary	3	3	4	5
Unknown	5	5	5	5

Recommendations: 1 - avoid combinations; 2 - usually avoid combinations; 3 - minimize risk; 4 - no action is required; 5 - there is no interaction. Source: Adapted from Tatro[22]

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Data analysis was performed using the Statistical Package for Social Sciences 15.0 (complex samples). First, the data were submitted to descriptive univariate analysis. For the quantitative variables, measures of central tendency and dispersion were calculated. The chi-squared test was used in the bivariate analysis to examine the association between benzodiazepine use and polypharmacy, and between polypharmacy and drug-drug interaction.

The study was approved by the Ethics Committee of the Federal University of Juiz de Fora, opinion no. 771.916, and a Free and Informed Consent Form was signed by all participants.

RESULTS

A total of 423 questionnaires were analyzed. Twenty-three participants were excluded from the study for failing the Mini-Mental State Examination and not having another respondent. Thus, the final sample consisted of 400 elderly persons.

With regard to drug therapy, 92.0% (368) of these elderly individuals were chronically using at least one drug (Figure 1). Of these, 48.4% made use of five or more drugs, characterizing polypharmacy. The mean number of drugs used by the participants was 4.8 (SD ±2.9).

Prevalence of benzodiazepine use in the population assessed was 18.3% (95% CI, 15.2 - 21.6) (73/400), who are the sample of interest for this study. The study sample was composed of 73 elderly persons who use benzodiazepine. In the bivariate analysis, benzodiazepine use was associated with polypharmacy (p<0.01; PR 3.03; 95% CI, 1.79-5.26). Most benzodiazepine users were women (74.0%), aged 70-79 years (45.2%), with 1-4 years of formal education (63.0%), self-reported as white (49.3%), and who resided with a companion (87.7%). The most widely used benzodiazepines were clonazepam (42.1%), bromazepam (19.7%), and alprazolam (15.8%). Additionally, 4.1% (3/73) of the elderly individuals used two benzodiazepines. Most (59.2%) of the benzodiazepines used by the study participants have a long elimination half-life (>24 h). Duration of benzodiazepine use was over six months in 85.5% of the users.

The number of medications chronically used by this group of elderly people ranged from 1 to 15, with a mean of 6.6 medications (SD ±3.2) per individual, and 141 different drugs identified. The most commonly used medications, according to the ATC classification, are described in Table 2. Higher prevalence values were observed for the use of drugs that act in the alimentary tract and metabolism (ATC A; 68.5%), in the cardiovascular system (ATC C; 89.0%), and in the nervous system (ATC N; 56.2%), with 38.4% also using antidepressants.

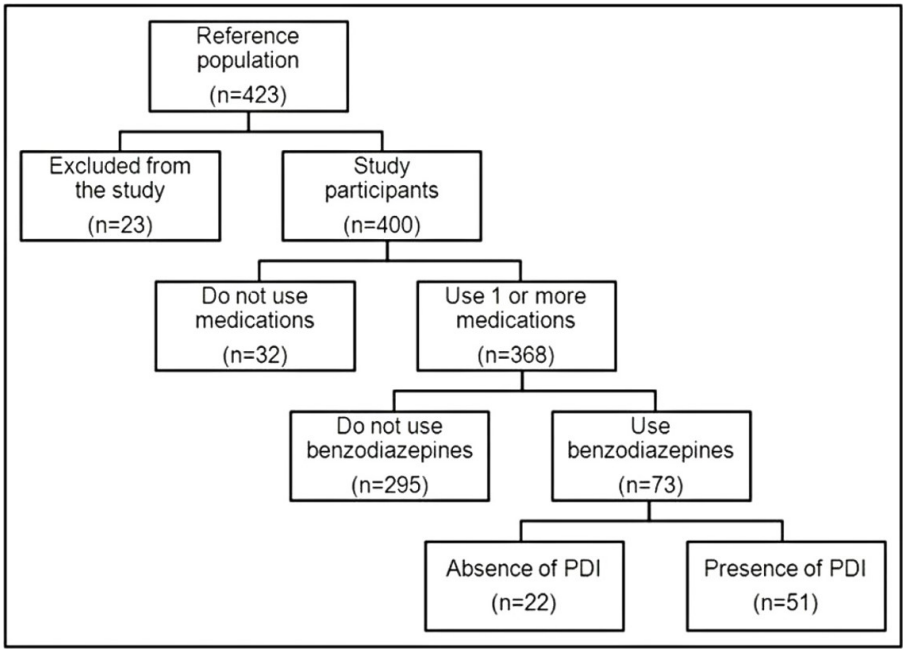

Figure 1. Reference population and study sample. PDI = potential drug interactions

Table 2. Most frequent medications among elderly users of benzodiazepines. Juiz de Fora-MG, Brasil, 2015

ATC Classification	Frequency (N=73) (%)
A - Alimentary tract and metabolism	
Calcium/Vitamin D	14 (19.2%)
Metformin	16 (21.9%)
Omeprazole	23 (31.5%)
B - Blood and blood forming organs	
Acetylsalicylic Acid	9 (12.3%)
C - Cardiovascular System	
Atenolol	14 (19.2%)
Furosemide	10 (13.7%)
Hydrochlorothiazide	19 (26.0%)
Losartan	30 (41.1%)
Simvastatin	22 (30.1%)
H - Systemic Hormonal Preparations	
Levothyroxine	14 (19.2%)

N = study sample; ATC = Anatomical Therapeutic Chemical

With regard to PDI in the elderly individuals who use benzodiazepines (n = 73) and other medications, 157 occurrences were found in 69.9% (n = 51) of them. Of these PDIs, there were 108 different types, and 25 were related to benzodiazepines. The number of interactions per patient ranged from 1 to 9, with a mean of 2 PDIs per patient (SD ±2.16). In the elderly individuals who use benzodiazepines, polypharmacy was associated with PDI (p<0.01; PR = 16.13; 95% CI, 4.67-55.55).

The most frequent PDIs are shown in Table 3. The frequencies of PDI occurrences by classification of severity, documentation, and clinical value are shown in Table 4. It is noteworthy that 92.3% of the PDIs were considered highly significant, with a clinical value of 1 or 2.

Table 3. Most frequent drug interactions in elderly users of benzodiazepines. Juiz de Fora-MG, Brasil, 2015

Potential drug interactions	N (=73)	Severity	Documentation	Clinical value
Levothyroxine-omeprazole	7	Moderate	Good	2
Alprazolam-omeprazole	6	Moderate	Fair	2
Calcium levothyroxine	5	Moderate	Excellent	2
Insulin-losartan	5	Moderate	Fair	2
Levothyroxine-simvastatin	5	Moderate	Good	2
Ginkgo biloba-omeprazole	4	Moderate	Good	2
Atenolol-calcium	3	Secondary	Good	3
Calcium-hydrochlorothiazide	3	Moderate	Fair	2
Captopril-furosemide	3	Moderate	Good	2
Diazepam-omeprazole	3	Secondary	Good	3
Insulin-metformin	3	Moderate	Fair	2

N = number of patients who experienced an interaction at least once. Regarding clinical value: 2 = usually avoid combination; 3 = minimize risk

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Table 4. Potential Drug Interactions by classification of clinical value, severity, and documentation. Juiz de Fora-MG, Brasil, 2015

Clinical Value	Severity	Documentation	N=157 (%)
1	Contraindicated/ Important	Excellent/Good/Fair	38 (24.2%)
2	Moderate	Excellent/Good/Fair	107 (68.2%)
3	Secondary	Good/Fair	12 (7.6)

N = number of iterations; 1 = avoid combination; 2 = usually avoid combination; 3 = minimize risk

DISCUSSION

Prevalence of benzodiazepine use in the population studied was 18.3%, corroborating the literature[22,24]. The prevalence of psychotropic drug use observed in a municipality of the state of Minas Gerais city was 13.4%; specifically, 8.3% for benzodiazepines[25].

The high consumption of benzodiazepines may be related to the gradual reduction in human resistance to stress tolerance, the introduction of new drugs, the growing pressure from advertising by the pharmaceutical industry, or even to inappropriate prescribing habits of professionals[26]. In addition to the fact that medications are considered one of the main contemporary healthcare technologies, promising to avert any suffering from today's society, such as depression, anxiety, psychotic disorders, loneliness, economic crises and sadness, simply by administering an effective chemical substance into the body[27].

The long-term use of these drugs in 85.5% of these elderly individuals and the high prevalence of long half-life benzodiazepines (59.2%) are noteworthy. Benzodiazepines are considered unsuitable for elderly patients, regardless of drug half-life[9,10]. The literature suggests that even short-acting benzodiazepines are a significant risk factor associated with frequency of falls in geriatric patients[28].

In the present study, the use of benzodiazepines was associated with polypharmacy. This practice is common among older people for various reasons, such as increased life expectancy, prevalence of chronic degenerative diseases with complex pharmacotherapeutic regimes, introduction of new drugs on the pharmaceutical market, self-medication, and improper use of drugs[29].

A cross-sectional study conducted with community-dwelling elderly people found a polypharmacy prevalence of 32% and observed positive association with female gender, increased age, negative self-rated health, and medical consultation in the past three months[6].

Although the use of multiple medications may be appropriate and necessary to optimize medical conditions or quality of life, polypharmacy can expose patients to the risk of serious consequences due to pharmacokinetic and pharmacodynamic changes associated with age[5]. Polypharmacy is the main factor responsible for adverse drug-related events and reactions, and DI represents the most directly related consequences[4].

Polypharmacy and potentially inappropriate drugs are a major concern for the drug safety of elderly patients, potentially leading to DI[29]. In the participants of present study, polypharmacy was associated with PDI. The occurrence of PDI in the elderly individuals who use benzodiazepines was high (69.9%). The highly significant interactions (clinical value 1 or 2) are noteworthy, with a prevalence of 92.3%, and the concomitant use of drugs should be avoided as much as possible. As per the 2019 Beers-Fick criteria, interactions are highly associated with clinically relevant adverse events, and should be avoided among older adults[9]. The clinical consequences of using inappropriate medicines are important for public health due to the risk of adverse events and a negative impact on the functionality of elderly individuals[30].

Among the PDIs, 15.9% were related to the use of benzodiazepines. In most cases, a clinical result of these PDIs is the increased risk of benzodiazepine toxicity, including central nervous system depression, somnolence, dizziness, ataxia, lethargy, hypotension, and psychomotor impairment[21]. A population-based study showed a prospective contribution of psychotropic drug use to the development of functional disabilities in the elderly population. This association ranged according to gender and number and class of used psychotropic drugs. For the female

stratum, the use of benzodiazepines represented a risk factor to the development of functional disability for instrumental activities of daily living[31].

Other interactions, such as concomitant use of diazepam and phenobarbital, bromazepam and quetiapine, and bromazepam and flunitrazepam, can lead to increased risk of respiratory and cardiovascular depression[21].

Elderly persons susceptible to the DI related to benzodiazepines have a greater chance of hospitalization, and represent a greater financial expense for the health service[32]. In addition, there is a strong association between the number of drugs used and the likelihood of a severe or clinically relevant PDI[33]. "Potential Drug Interaction" refers to the possibility of one drug altering the effect of another one administered concomitantly, independent of the occurrence of adverse events, and can occur before (physicochemical interaction or incompatibility) or after administration[34]. Variables such as clinical conditions of individuals and number and characteristics of the medications are related to the prevalence and possible consequences of DI[4].

A study conducted at a mental health outpatient clinic found polypharmacy coexisting in 75% of the prescriptions containing benzodiazepines for the elderly patients, and only a minority of these prescriptions were rational[35]. The consequences of the widespread use of medications have impact in the clinical and economic contexts, and repercussions on patient safety[4].

Drug toxicity in the elderly population is a reality, and can be the deciding factor for preventive interventions[33]. The interventions should involve both hospitals and primary care, minimize the number of drugs prescribed for elderly individuals, maintain the simplest possible dosing scheme, and be focused primarily on reducing unnecessary polypharmacy[33,36]

Pharmacists can play an important role in the management of the drug therapy of elderly patients, as they have comprehensive knowledge about the patients' medications, including non-prescribed drugs and drugs prescribed by different specialists [3.] Prescribers, as well as pharmacists, should be aware that each drug added to a therapeutic regimen increases the risks of PDI[5,23,32,36]. In addition, there has to be adequate interaction between the members of the health team, aiming at a safe pharmacotherapy and rational use of medicines.

Given the high frequency of drug interactions and polypharmacy, there is an evident need for an approach that ensures safe drug therapy for older adults[7]. Strategies may consider possible therapeutic alternatives and patient monitoring. Interventions conducted by pharmacists within this practical setting, such as drug therapy reviews and actions planned with the prescriber, may reduce the number of older patients with clinically relevant drug interactions[7].

A limitation to this study is the identification of PDIs through a database, which does not mean that the possible adverse events related to the interaction are manifested clinically in patients. Each PDI flagged in the database should be evaluated on a case-by-case basis in relation to their clinical relevance, considering the drug dosage, therapy duration, severity and frequency of the adverse reaction associated with the interaction, and risk factors related to the patient. Other limitations include the difficulty in establishing a cause-effect relationship with the cross-sectional study design and self-reported measures, through this study it would be possible to know associations between the variables. The advantages of this study should also be highlighted, such as the fact that it was carried out with elderly community-dwelling persons, who are less prone to selection bias.

The occurrence of PDI in the study population was associated with the number of drugs used. The occurrence of PDI was high in patients using benzodiazepines, including interactions of highly significant clinical value, reinforcing the importance of assessing the drug use process. The detected interactions can present and induce adverse reactions, compromising the safety of pharmacotherapy for elderly individuals. Recognition of PDI enables the prevention of therapeutic failure situations, minimizing risks.

In elderly patients, it is not always possible to reduce the number of prescribed medications, mainly due to the numerous comorbidities that afflict this population. Strategies to minimize the risks of DI include selection of appropriate drug therapy and continuous monitoring of the patient and of possible adverse events using an individualized assessment. This study contributes to the knowledge about the profile of DI in elderly users of benzodiazepines, becoming increasingly important for planning actions aimed at patient safety.

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