Full length Research paper

Evaluating the frequency in the use of multiple concomitant medications in Alzheimer's disease

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Alzheimer's disease (AD) affects a large portion of the elderly worldwide and is the most common dementia in this population. AD is usually accompanied by concurrent comorbidities leading to the simultaneous use of several drugs to improve the quality of life, which renders AD patients vulnerable to drug interactions and adverse reactions. This study assessed the frequency of polypharmacy based on comorbidities in AD patients from the city of Guarapuava, Paraná, Brazil. This is a cross-sectional study in non-institutionalized and volunteer AD patients. The Clinical Dementia Rating (CDR) scale was applied to classify the AD stage and a socio-economic survey was used to identify possible comorbidities and medications taken. Medications were evaluated according to the Kussano's criteria (2010) to identify polypharmacy. The incidence of polypharmacy was high (up to 65.9%, n = 27); hypertension was the most frequent comorbidity (58.54%, n = 24). AD patients inappropriately take drugs, either because of inattention or lack of popular medical understanding and may be subjected to consequences such as drug interactions and iatrogenic adverse reactions. Hence, studies focusing on AD patients investigating further risks caused by drug interactions are relevant and can increase awareness in their health care assistance and caregivers.

Key words: Alzheimer's disease, polypharmacy, iatrogeny, adverse reactions.

INTRODUCTION

The number of people over 65 years old has grown significantly in the last decades in Brazil (Silva et al., 2012; Secoli, 2010). According to the Brazilian Institute of Geography and Statistics (IBGE), the population in this age group should increase from 14.9 million (7.4% of the total population) in 2013 to 58.4 million (26.7% of the total

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population) in 2060, with a life expectancy of 81 years. This estimate represents four times the current elderly population in Brazil. Other figures show that about one in five Americans will be over 65 years old in 2030, which leads to the estimation that 88.5 million Americans will be 65 years and older in 2050 (Oster and Oster, 2015). This increased life expectancy has resulted from the emergence of new primary prevention programs for diseases and advances in medical technology (Silva et al., 2013).

An increase in the occurrence of diseases associated with senility occurs with an increase in life expectancy. Thus, Alzheimer's disease (AD) appears as the most common dementia affecting more than 20 million elderly worldwide (Pinheiro et al., 2013). Dementias are often accompanied by comorbidities such as diabetes, hypertension, congestive heart failure and deglutition disorders among others (Caixeta et al., 2012) and can affect about 40 to 56% of people with cognitive decline (Martín-Garcia et al., 2013).

Due to the pathological process of dementia and its comorbidities, the concurrent use of daily multiple medications becomes common practice to improve the quality of life in this group (Silva et al., 2012; Kusano, 2009; Pinheiro et al., 2013; Quinalha and Correr, 2010; Secoli, 2010). This practice makes the elderly more vulnerable to adverse effects that can result from taking multiple drugs (Kusano, 2009; Ribeiro et al., 2014).

Concomitant use of multiple drugs is called polypharmacy and it can be classified as mild, moderate or severe according to the number of drugs used by the patient. The mild condition is defined as the use of two or three drugs, the moderate condition as the use of four to five drugs, and the severe as the use of more than five drugs (Silva et al., 2012; Kusano, 2009). Some studies have demonstrated that the prescription of more than two drugs can provoke adverse reactions due to drug interactions between active ingredients or formula components such as excipients and flavoring agents (Colette et al. 2011; Tavares et al., 2013).

Based on the possibility of the occurrence of polypharmacy and the lack of studies evaluating the frequency in the use of multiple concomitant medications, this study assessed the frequency of polypharmacy according to the occurrence of comorbidities in AD patients who are residents of the city of Guarapuava, Paraná, Brazil.

MATERIALS AND METHODS

The study followed the quantitative order of the cross-sectional type. The sample consisted of elderlies assisted at the Unified Health System (SUS) in the city of Guarapuava, Paraná, Brazil, who were identified through the computerized system of the Information Technology and Communication Company of Paraná (CELEPAR®). The study was approved by the Ethics Committee on Research involving humans from the Midwest State University

under the opinion number of 6111316/2014.

After data collection in the system, the elderlies were contacted by phone to arrange for home visits between January and October 2014. The Voluntary Informed Consent Form - TCLE – was delivered and signed by the corresponding patients' guardians or caregivers. The final disease diagnosis was made through a histological examination of postmortem brain tissue. Thus, the American Psychiatric Association (DSM) and the "National Institute for Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association" (NINCDS-ADRDA) recommend that the life diagnosis of dementia should be performed through a proper research-based history and general physical examination. In this study, the most cited neurological examination, the "Clinical Dementia Rating" (CDR) (Oliveira et al., 2008) was used to track the disease stage. This rating is divided into CDR 1, CDR 2, and CDR3, which indicate the dementia severity as mild, moderate and severe, respectively.

The sociodemographic questionnaire, which was structured to draw the study population's profile, was also applied to identify existing comorbidities, and drugs, dosage and frequency of usage. All the drugs, whether prescribed or self-medicated, were included in the study. Polypharmacy was classified according to Kusano (2009) as mild (use of two or three drugs), moderate (use of four or five drugs) and severe (use of more than five drugs).

The sample inclusion criteria were the presence of AD diagnosed by a geriatrician or neurologist, and participation in the "Specialized Component of Pharmaceutical Assistance" program (CEAF) provided by the 5th Regional Health of Guarapuava, Paraná. The exclusion criteria were patient not found after three home visits and death before study completion.

Data were analyzed using the SPSS version 20.0 statistical package for Windows®. The results were presented in relative and absolute frequencies. The Chi-square test, Fisher's exact test, and Pearson correlation coefficient were used to investigate possible associations. The significance level of $P < 0.05$ was adopted.

RESULTS

Out of the 57 AD patients initially selected, 8 (14.04%) were not found, and 8 (14.04%) died before the study completion; results were obtained for 41 (71.93%) patients. The sociodemographic data from these patients are presented in Table 1.

Polypharmacy was identified in 65.9% (n = 27) of the patients, mostly occurred in groups CDR 2 and 3 (Table 2) and resulted from simultaneous administration of drugs due to the presence of comorbidities. The Pearson linear correlation coefficient indicates a moderate correlation between polypharmacy incidence and lack of incidence.

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One of the pharmacological strategies in the treatment of AD is making use of acetylcholinesterase enzyme inhibitors when two drugs are the main treatment protagonists; in this study (Table 4), more than half of the elderlies (54.84%, n = 17) used the drug Donepezil hydrochloride.

According to the drugs used for self-declared patho-

Table 1. Sample design.

Gender	Percentage	Mean age	CDR		
			1	2	3
Male	39.02% (n=16)	79.27 ± 8.20	18.75% (n=3)	37.5%(n=6)	43.75% (n=7)
Female	60.98% (n=25)	77.70 ± 14.12	12% (n=3)	40% (n=10)	48% (n=12)
		Total	14.64% (n=6)	39.02%(n=16)	46.34% (n=19)

Data presented as mean ± standard deviation; relative frequencies.

Table 2. Correlation between polypharmacy and the CDR scale.

Polypharmacy	CDR 1	CDR 2	CDR 3	P
	Mild	Moderate	Severe	
No	4.9% (n=2)	9.8%(n=4)	19.5% (n=8)	0.678
Yes	9.8% (n=4)	29.3%(n=12)	26.8% (n=11)	

Data presented as relative frequencies; Pearson linear correlation coefficient through the Chi-square and Fisher's exact tests.

logies, hypertension was the most frequent comorbidity in these elderlies, with 24 (58.54%) cases (Table 5). The comorbidities with the lowest incidences were Parkinson's disease and stroke, with 7 (17.7%) cases with each disease.

DISCUSSION

The current study findings corroborate with those reported by Lucchetti et al. (2010) and Hanlon et al. (2009). Lucchetti studied a sample of 209 patients in a Brazilian hospital and verified the occurrence of polypharmacy in 46.4% (n = 97). In this same study, 67.9% of the patients (n = 142) were affected by hypertension and used cardiovascular, psychotropic, anticonvulsant and antidepressant drugs. Hanlon et al. (2009) observed the occurrence of 74% polypharmacy when studying 113 care institutions in the United States. Therefore, it is evident that the elderly are, in general, potentially susceptible to the risk of adverse effects caused by drug interactions and idiosyncratic reactions (Nguyen, 2006).

Carvalho et al. (2012) observed that the high prevalence of polypharmacy in elderlies was due to the presence of chronic non-transmissible diseases (NTDs) when studying 2,143 elderlies and observed that 36% of the group took more than five drugs, which is characterized as severe polypharmacy. This result is consistent with our study; elderlies suffer from multiple medical problems, including AD, which affects the quality of life. So, polypharmacy could be expected in the elderly population at large, not only elderly AD patients. Polypharmacy could be more dangerous to AD patients

because of their dementia. According to Rozenfeld et al. (2008), diseases such as hypertension, heart diseases, rheumatic diseases and diabetes indicate the potential for polypharmacy because patients with these diseases need several medications with proven effectiveness in order to achieve health improvement. This assumption explains the high number of cases found in this study.

By comparing the drugs used in this study with the criteria of Beers et al. (1991), it was detected that some drugs, such as benzodiazepines (Alprazolam and Diazepam), antidepressants (Fluoxetine), antihistamines (Cyproheptadine) and some antihypertensive (Doxazosin) are used inappropriately, imposing a high degree of side effects and drug interactions. Such substances could be replaced by others that are appropriate for the treatment and do not cause potential side effects. Furthermore, according to the classification of Secoli (2010), some interactions among the most common classes of drugs were identified in this study such as between the antihypertensive captopril and the diuretic hydrochlorothiazide, and between the antiarrhythmic amiodarone and the anticoagulant Warfarin; the potentiation of these drugs by the concomitant use of captopril leads to inhibition of cytochrome P450.

Hypertension is the most common comorbidity in the elderly population as shown in Table 5. According to Regalado Doña et al. (2009), this constitutes a risk factor for those with vascular disease and AD. In this study, more than half of the elderlies suffered from hypertension and required blood pressure treatment with drugs. The smallest possible number of drugs should be used considering the iatrogenic/benefits risk ratio. Based on the risks, caution in choosing the anticholinesterasic drug

Table 3. Pharmacological classes most frequently used by AD patients in the city of Guarapuava, PR.

Class	Number of individuals	%
Antihypertensive	32	78.05
Anticholinesterasic	30	73.17
Antiparkinsonian	21	51.22
Antidepressant	18	43.90
Antidiabetic	18	43.90
Analgesic	17	41.46
Antipsychotic	16	39.02
Antihyperlipidemic	12	29.27
Supplement	10	24.39
Antiulcer	9	21.95
Diuretic	9	21.95
Anticonvulsant	6	14.63
Antiplatelet	5	12.20
Vasodilator	5	12.20
Anxiolytic	5	12.20
Thyroid hormone	5	12.20
Antiarrhythmic	4	9.76
Antithrombotic	4	9.76
Alpha-blocker	3	7.32
Anti-alopecia	2	4.88
Others	16	39.04

Data presented as relative frequencies.

Table 4. Anticholinesterasics used by the studied elderlies.

Drug	Number of individuals	%
Donepezil hydrochloride	17	54.84
Rivastigmine hemitartrate	13	41.94

Data presented as relative frequencies.

Table 5. Observed comorbidities.

	Number of individuals	%
Hypertension	24	58.54
Diabetes	12	28.27
Hypercholesterolemia	11	26.83
Cancer	8	19.51
Parkinson's disease	7	17.7
Cerebrovascular accident	7	17.7

Data presented as relative frequencies.

is necessary to avoid the prescription of those drugs in this class that has a central action on cholinesterase receptors (Caixeta et al., 2012).

In the case of less prevalent comorbidities, our data showed inconsistencies in data from Tables 3 and 5; most of the elderlies took antiparkinsonian medications (Table 3), however, Parkinson's disease was one of the least recurring among self-reported diseases (Table 5). This is due to the fact that the vast majority of our patients and caregivers had a low level of education (data

not shown), indicating the lack of information on drugs and their pharmacological actions in addition to the lack of attention or difficulty in understanding medical language. Laffa et al. (2013) observed this fact in their study where low education was significantly correlated with noncompliance with dosage (p = 0.009) suggesting difficulties related to the identification of drugs and administration techniques.

Cholinesterase inhibitors (IChE) are frequently used for the treatment of mild to moderate stages of AD (Forlenza, 2005; Fagherazzi et al., 2009). The prevalence of the use of the long-term medication, donepezil hydrochloride, was observed within this pharmaceutical class. Montastruc et al, (2013) also showed a high prevalence of donepezil use in a study that evaluated 684 elderlies: 610 of these were using some anticholinesterasic and, among these, 63% (n = 431) used donepezil. The prescription of this drug is quite frequent because this cholinesterase inhibitor presents low risks as compared to other IChEs; furthermore, it's the selectivity of donepezil results from prevention of peripheral side effects recurrent of its activity, its action time, and because its use is reversible preventing major risks in the event of poisoning (Lima, 2008).

Goes et al. (2015) assessed the nutritional status of a group of patients evaluated in the same city as this study and verified that most of the patients were using Donepezil and were in a state of malnutrition with low albumin levels. Because this drug requires interaction with albumin, the level of free molecules increases in patients with low albumin levels; these free molecules interact with other drugs such as some with cardiovascular activity.

Out of the 41 patients diagnosed with AD (in this study), only 34 (82.93%) use anticholinesterasic inhibitors. According to the Ministry of Health (2010) in the public consultation No. 15 of March 31, 2010, only patients with CDR equal to or less than 2 are entitled to free medication for care continuity at the Unified Health System (SUS) in Brazil. This medication withdrawal is justified by the fact that, even with the pharmacological approach being only symptomatic, the medication is ineffective due to the progressive degenerative characteristic of the disease (Forlenza, 2005). However, there are studies that indicate that the quality of life of the elderly in this scenario would be compromised because the degenerative disease processes accelerate the mental and functional decline, affecting the quality of life of patients and caregivers, even in the most advanced stage of AD (Inouye et al., 2010).

Hence, it is concluded that polypharmacy is present in the daily life of the elderly population with AD, and in greater numbers in populations with some type of NTD. However, this fact can lead to harmful consequences such as drug interactions, iatrogenic and adverse reactions among others. It was also evidenced that some of the studied elderlies make use of inappropriate drugs, either due to inattention or lack of medical knowledge.

Further studies investigating the interactions caused by these drugs and the consequences of these interactions with the patients will significantly contribute to preventing the occurrence of polypharmacy. These studies could also reinforce the need for guidance and pharmaceutical care on such drugs which could increase the awareness in the population of caregivers.

Conflict of Interests

The authors have not declared any conflict of interests.

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