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Research Article

Drug Interaction in Institutionalized Elderly People

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Abstract

Introduction: The observation of drug interactions should be essential in geriatric pharmacotherapy, especially in frail elderly individuals. **Objective**: This study aims to analyze the drug interactions among elderly residents of a long-term care facility (LTCF). **Method:** This was an observational, cross-sectional and descriptive study of a philanthropic LTCF. All institutionalized residents were included, and daily prescriptions of continuous medications were observed. The possible interactions (major, moderate and minor) were identified using the *drugs.com platform*. The most frequent drug interactions were described, and their occurrence was analyzed according to sociodemographic and clinical variables. **Results**: The prescriptions of 89 individuals aged 60 to 102 years were analyzed. The presence of at least one major drug interaction was observed in 38 prescriptions (42.7%), moderate drug interactions in 75 (84.3%) and minor drug interactions in 43 (48.3%). Among individuals with five or more medications, the frequency of major drug interactions was 51.9%, and among those who used eight or more drugs, it was 69.8%. A significant association was observed between the occurrence of major drug interactions and longer institutionalization time (p=0.025). Associations with age groups, gender and functionality were not significant. The major drug interactions identified were amlodipine/simvastatin (9), amlodipine/phenytoin (7) and omeprazole/cilostazol (5). The drugs most often involved in higher drug interactions were amlodipine, topiramate, haloperidol, promethazine and simvastatin. **Conclusion:** The results show a high possibility of drug interactions with a risk of adverse events in vulnerable elderly individuals. They also reveal that the most important drug interactions were observed with drugs frequently used in clinical practice.

Keywords: Aged; Drug interactions; Homes for the aged; Polypharmacy

Introduction

In recent decades, there has been an increase in life expectancy and subsequently, chronic degenerative diseases, which has contributed to the increased use of multiple drugs with potential adverse effects, especially in more vulnerable populations, such as elderly individuals [1].

There are many senescent changes that make the elderly population a more vulnerable group. The use of multiple drugs can be a major clinical problem in elderly individuals with cognitive decline, organ dysfunction, functional disability and frailty [2].

Polypharmacy, even when necessary, can generate complications for users due to the iatrogenic potential of each drug, as well as the possibility of drug interaction in which a substance can interfere with the action or metabolism of another concomitant drug [3]. These interactions have long been recognized as potentially responsible for unexplained adverse effects [4]; however, they are still little explored in epidemiological studies [5,6].

Drug interactions can be pharmacokinetic when a drug interferes with the absorption, distribution, metabolism or excretion of another drug. The main mechanism of a drug interaction of metabolic origin stems from the different affinities to the enzymatic system of cytochrome P450 [7]. When there is a change in the action of a drug in response to another, a pharmacodynamic

drug interaction has occurred. These interactions may have a synergistic, additive or antagonistic action [8].

Recently, many digital tools for the identification of drug interactions have been made available to assist in the efficacy of pharmacotherapy. These programs are based on different drug databases and can contribute to the qualification and safety of polypharmacy prescriptions. However, they are not yet widely used [9-11].

The improvement of pharmacological therapy in more vulnerable elderly groups has received greater attention from researchers, but they often focus on the definition of appropriate drugs and the prescription of certain pharmacological groups. Some studies have analyzed the occurrence of possible drug interactions in elderly individuals in general [12]. However, there is a need for a better understanding of drug interactions in groups of elderly individuals with greater pharmacological complexity, such as residents of long-term care facilities (LTCF), especially.

The objective of this study is to evaluate the prescriptions used by institutionalized elderly individuals and to identify possible drug interactions that leave them vulnerable to adverse events.

Methodology

This was a cross-sectional, observational and descriptive study conducted in an LTCF operated by a charity. The LTCF does not have a specific clinical care program, and elderly residents are treated by various public health services. The prescriptions of all 89 residents were reviewed in January 2022, and only the medications prescribed for continuous use were analyzed. The following variables were considered: age, sex, length of institutionalization, degree of functional dependence and continuous use of medications.

The residents of the LTCF are housed in two different wards according to the level of functional dependence: a) less dependence - individuals who are able to perform basic activities of daily living (ADLs); b) greater dependence - individuals with impaired locomotion and total dependence on basic and instrumental ADLs.

To identify the presence of drug interactions, the digital database freely available on the internet at *drugs.com* was used. In this drug interaction checking tool, all drugs in continuous use are recorded, and four different diagnoses of drug interaction are identified: 1) major drug interactions - clinically significant and important reactions, which should be avoided because the risk does not outweigh the benefit; 2) moderate drug interactions - significant and moderate reactions that could be used in some specific situations; 3) minor drug interactions - minimal clinical changes that, depending on the situation, could suggest drug changes; 4) no identified interaction [13].

All identified drug interactions (major, moderate and minor) were presented quantitatively according to age group. The largest drug interactions were discriminated according to the frequencies observed and analyzed according to sex, age group (60 to 75, 76 and older), length of institutionalization (up to 4 years, 5 years or more), and number of drugs used continuously: polypharmacy (5 or more drugs and 8 or more drugs). The 10 drugs most often involved in higher drug interactions are depicted in descending order.

The data were analyzed using SPSS software, with a 95% confidence interval (CI). The study was approved by the LTCF and ethical commtee, and the results and suggestions for adjustments in pharmacotherapy were presented and discussed with the staff.

Results

The prescriptions of 89 individuals (54 men, 35 women) with a mean age of 76 years were analyzed with a standard deviation (SD)=8.3. Thirty-three elderly individuals were in the “less dependence” ward (37.1%), and 56 were in the “greater dependence” ward (62.9%). Half of the residents had been institutionalized for 5 years or more (Table 1).

The mean number of medications used continuously was 7.42, which was higher among women (8,17). The use of 5 or more medications daily was observed in 80.9% of elderly individuals, and 48.3% used 8 or more medications regularly (Table 1).

	Total (89)	Male (54)	Female (35)
Mean age – years (SD)	76.0 (8.3)	75.2 (7.8)	77.1 (9.0)
Age range			
60-75 years	41 (46.1%)	28 (51.9%)	13 37.1%)
>75 years	48 (53.9%)	26 (48.1%)	22 (62.9%)
Degree of functional dependence			
Less functional dependence	33 (37.1%)	23 (42.6%)	10 (28.6%)
Greater functional dependence	56 (62.9%)	31 (57.4%)	25 (71.4%)
Length of institutionalization			
0 – 4 years	45 (50.6%)	30 (55.5%)	15 (42.9%)
5 or more years	44 (49.4%)	24 (44.4%)	20 (57.1%)
Number of daily drugs - mean (SD)	7.42 (3.3)	6.90 (3.3)	8.17 (3.3)
Polypharmacy – 5 or more drugs	72 (80.9%)	41 (75.9%)	31 (88.6%)
Polypharmacy – 8 or more drugs	43 (48.3%)	24 (44.4%)	19 (54.3%)
SD: Standard Deviation			

Table 1: Characterization of analyzed population in according to sex.

The presence of at least one major drug interaction was observed in 38 prescriptions (42.7%), and the possibility of moderate and minor drug interactions was observed in 75 (84.3%) and 43 (48.3%) prescriptions, respectively. The subjects had an individual average of 8.9 moderate drug interactions, and more than 10 moderate drug interactions were observed in 31.5% of them. The occurrence of at least two major drug interactions was identified in 18.0% of the individuals, and 11 elderly individuals (12.3%) had three or more major drug interactions (Table 2).

	Total (89)	60-75 years (41)	>75 years (48)
Major drug interaction (n)			
0	51 (57.3%)	23 (56.1%)	28 (58.3%)
1	17 (19.1%)	6 (14.6%)	11 (22.9%)
2	10 (11.2%)	8 (19.5%)	2 (4.2%)
3	5 (5.6%)	1 (2.4%)	4 (8.4%)
4	5 (5.6%)	3 (7.3%)	2 (4.2%)
5	1 (1.1%)	0	1 (2.1%)
Moderate drug interaction (n)			
0	14 (15.7%)	7 (17.1%)	7 (14.6%)
1 to 5	33 (37.1%)	16 (39.0%)	17 (35.4%)
6 to 10	14 (15.7%)	7 (17.1%)	7 (14.6%)
11 to 20	20 (22.5%)	7 (17.1%)	13 27.1%)
>20	8 (9.0%)	4 (9.8%)	4 (8.3%)
Moderate drug interaction (median)	8.4 (9.6)	8.8 (11.5)	8.0 (7.8)

Table 2: Frequency of major and moderate drug interactions in according to age range.

Among the individuals with major drug interactions, there was no significant association with age or sex. Higher frequencies of major drug interactions were identified among residents with greater functional dependence (not significant) and among those with longer institutionalization times. Among the individuals who used at least 5 medications daily, the frequency of major drug interactions was 51.4%, and among those with 8 or more medications, it was 69.8% (Table 3).

	Total (89)	**Major Drug Interaction**	
		yes (38)	**no (51)**
Age range			
60-75	41 (46.1%)	18 (47.4%)	23 (45.1%)
75+	48 (53.9%)	20 (52.6%)	28 (54.9%)
Age (years)	76.0 (8.3)	75.7 (9.3)	76.2 (7.6)
Sex			
Male	54 (60.7%)	21 (55.3%)	33 (64.7%)
Female	35 (39.3%)	17 (44.7%)	18 (35.3%)
Functional dependence			
Less dependence	33 (37.1%)	11 (28.9%)	22 (43.1%)
Greater dependence	56 (62.9%)	27 (71.1%)	29 (56.9%)
Length of institutionalization			
0-4 years	45 (50.6%)	14 (31.1%)	31 (68.9%)
5 or more years	44 (49.4%)	24 (54.5%)	20 (45.5%)*
Polypharmacy (≥5 drugs)			
0-4	17 (19.1%)	1 (2.6%)	16 (31.4%)
5 or more	72 (80.9%)	37 (97.4%)	35 (68.6%) **
Polypharmacy (≥8 drugs)			
0-7	46 (51.7%)	8 (21.1%)	38 (74.5%)
8 or more	43 48.3%)	30 (78.9%)	13 (25.5%)**
*p<0.05 ** p <0.001			

Table 3: Distribution of major drug interactions in according to sex, age range, functional dependence, length of institutionalization and polypharmacy.

The most prevalent drug interaction was the association between amlodipine and simvastatin (9, 10.1%), followed by the combination of amlodipine with phenytoin (7, 7.9%), omeprazole with cilostazol (5, 5.5%), amlodipine with carbamazepine (4, 4.4%) and topiramate with promethazine (4, 4.4%) (Table 4). The ten main drugs involved in the occurrence of higher drug interactions were amlodipine (20), topiramate (13), haloperidol (11), promethazine (10), simvastatin (10), carbamazepine (9), phenytoin (9), and omeprazole (8), cilostazol (6) and risperidone (5).

Major drug interaction	N	%
Amlodipine and simvastatin	9	10.1
Amlodipine and phenytoin	7	7.9
Omeprazole and cilostazol	5	5.6
Amlodipine and carbamazepine	4	4.5
Topiramate and promethazine	4	4.5
Carbamazepine and haloperidol	3	3.4
Phenytoin and quetiapine	2	2.2
Haloperidol and promethazine	2	2.2
Haloperidol and risperidone	2	2.2
Topiramate and risperidone	2	2.2
Topiramate and chlorpromazine	2	2.2
Topiramate and metformin	2	2.2
Omeprazole and citalopram	2	2.2
Enalapril and losartan	2	2.2
Enalapril and spironolactone	2	2.2
Losartan and spironolactone	2	2.2
Promethazine and thioridazine	2	2.2
Amitriptyline and desvenlafaxine	1	1.1
Amitriptyline and fluoxetine	1	1.1
Carbamazepine and quetiapine	1	1.1
Carbamazepine and rivaroxaban	1	1.1
Cilostazol and rivaroxaban	1	1.1
Diazepam and olanzapine	1	1.1
Fluoxetine and imipramine	1	1.1
Haloperidol and chlorpromazine	1	1.1
Haloperidol and imipramine	1	1.1
Haloperidol and escitalopram	1	1.1
Haloperidol and periciazine	1	1.1
Imipramine and escitalopram	1	1.1
Imipramine and sertraline	1	1.1
Omeprazole and clopidogrel	1	1.1
Biperiden and topiramate	1	1.1
Topiramate and olanzapine	1	1.1
Topiramate and thioridazine	1	1.1
Promethazine and mirtazapine	1	1.1
Promethazine and citalopram	1	1.1
Propranolol and thioridazine	1	1.1
Risperidone and citalopram	1	1.1
Simvastatin and bezafibrate	1	1.1

Table 4: Characterization of major drug interactions.

Discussion

The results show a high frequency of possible drug interactions among elderly residents of an LTCF. Among individuals with polypharmacy, more than half have at least one possible major drug interaction. In addition, it is clear that the drugs involved in major drug interactions are drugs commonly used in clinical practice.

The study evaluated a very specific group of elderly people composed of residents of a philanthropic LTCF, who have socioeconomic limitations. Although this is a specific population in need of public assistance, it is very representative of the population of many LTCFs in developing countries; thus, the findings for pharmacological therapy have great clinical relevance.

Assis, et al. analyzed the prescriptions of elderly people in philanthropic LTCFs in Brazil and observed a profile similar to that of this study, with a predominance of males, mean age of 77 years and use of 5 or more drugs in 78% of subjects [14]. In another analysis of LTCF in Brazil, polypharmacy was identified in only 33.6% of prescriptions [15].

The identified drug interactions were classified by the potential for adverse events. Higher drug interactions, which have a high risk of complications, were observed in 42% of elderly individuals, and moderate drug interactions were observed in 85%. This high frequency of drug interactions suggests that in this group of elderly individuals, many of the common problems related to functional decline, cognitive disorders, decompensation by underlying diseases and other complications could be associated with the presence of a drug interaction.

The occurrence of drug interactions was also observed in elderly patients by other researchers, whose frequency varies according to the profile of the individuals analyzed [16]. In hospitalized elderly individuals, the frequency of at least one higher drug interactions was 54% [17]. Based on the results of a systematic review, Bories, et al. observed a significant frequency of drug interactions in 28.9% of hospitalized elderly and 4.3% and 3.3% in primary care institutions and LTCFs, respectively [18]. A study in Spain with polymedicated elderly aged 65 to 74 years in primary care found that 50.1% had at least one drug interactions [12]. In noninstitutionalized elderly individuals, this frequency was 22.5% [19].

The vast majority of drug interactions studies in the elderly population were conducted in more developed countries, and these researchers observed a lower frequency of relevant drug

interactions in institutionalized elderly individuals compared to community-dwelling and hospitalized elderly individuals [18,20]. This is justified by the structure of the LTCFs in developed countries that have better clinical and pharmaceutical care conditions than the LTCFs of less developed countries such as Brazil.

The patients with the possibility of higher drug interactions were the individuals with the longest institutionalization time. It is noteworthy that in welfare LTCFs, there are a large number of patients with disabling psychiatric diseases who are institutionalized early in the course of their illnesses.

The results analyzed in the present study did not show a significant association between age group and sex with an occurrence of higher drug interactions. The demonstration of these associations varies greatly with the profile of the analyzed population and the standard of pharmacotherapeutic care offered by institutions. Analyses have been performed in which the frequency of drug interactions in elderly individuals varies according to sex and age group [20] and others in which this does not occur [19].

As predicted, the higher the use of continuous medicines was, the greater the possibility of drug interactions. The data showed that 7 out of 10 individuals with more than 8 daily medications have a greater possibility of drug interactions. Other authors have also observed the great importance of polypharmacy in the possibility of drug interactions [12,15,19]. This strengthens the need for health professionals who assist the elderly with polypharmacy to be vigilant for the possibility of drug interactions.

Among the frequent drug interactions identified, the concomitant use of amlodipine and simvastatin was the most prevalent in this study (10.1%) and also observed in 5.2% [12] and 2.6% [21] in the elderly population by other authors. Calcium channel blockers (CCBs) have a known drug interaction capability and, in this case as CYP34A enzyme inhibitors, may generate impaired metabolization of simvastatin, increasing the chance of adverse events [5].

Other associations involving CCBs included the use of amlodipine, phenytoin and carbamazepine. These two anticonvulsants have an action of inducing metabolism, which may lead to complications in vulnerable elderly individuals, especially in those with reduced renal function [22].

Statins, widely prescribed for elderly individuals due to evidence of their efficacy in the control of dyslipidemias and in the prevention of cardiovascular events, have a great potential for drug interactions [23]. In order to minimize these adverse events arising from drug interactions, it is imperative to always review the relevance of the use of statins in each clinical situation and avoid the association of drugs that potentiate their undesirable effects.

Another pharmacological group that has received attention in pharmacotherapeutic practices is proton pump inhibitors [24]. These drugs are recognized for the great potential of drug interactions, either by interference in gastric ph compromising the absorption of some drugs or by affinity to enzymes CYP2C19 [25]. In the present study, the association of omeprazole with cilostazol was identified in five individuals and could present important side effects related to higher serum cilostazol concentrations.

When analyzing the most identified drugs in the higher drug interactions, anticonvulsants, neuroleptics, amlodipine, simvastatin and omeprazole stand out. Psychoactive drugs have been the focus of attention in prescriptions among elderly individuals [26], especially those in institutions, where their use is more widespread [27,28]. Psychotropic drugs were reported to be responsible for 35% of the drugs involved in drug interactions among outpatients [29]. Neuroleptics are the most widely used psychoactive drugs in ILPIs and contribute to an increased risk of arrhythmias and nervous system depression when in combination with other drugs [5].

In relation to the main drugs involved in larger drug interactions, similar data were obtained by researchers in Brazilian philanthropic LSI, with the use of haloperidol, benzodiazepines and phenytoin [30]. Moreover, in the non-institutionalized elderly population in Ireland, the main drugs involved in relevant drug interactions were warfarin, escitalopram, atorvastatin and furosemide [19].

A very important aspect in studies on drug interactions is the discrimination of the database that is used in the identification of drug interactions. Some authors have analyzed the efficacy and accuracy of the main programs, however these tools are impossible to access freely [9,10]. A platform used in this study, *drugs.com*, is freely accessible and is also widely used in clinical practice. In this program, the drugs in concomitant use are analyzed and the interactions are identified and classified into three levels of clinical importance, followed by guidance and suggestions for health care providers [13].

Despite some limitations related to the restricted profile of the elderly studied and the database of drugs used to check drug interactions, we recognize the importance of this study in the context of geriatric pharmacotherapy. The data highlight the need to identify the possibilities of drug interactions in patients with multiple medications.

Furthermore, they present the reality of long-stay institutions that are different from those usually studied in the international literature. It is noteworthy that these philanthropic LTCFs have material and human resource limitations that challenge health professionals at the time of prescription.

In conclusion, polypharmacy in an institutionalized geriatric population should be discouraged. Rationalization of pharmacotherapy is necessary, avoiding adverse events that could compromise the quality of life of these vulnerable individuals.

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