CLINICAL SCIENCE

Gender differences, polypharmacy, and potential pharmacological interactions in the elderly

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OBJECTIVE: This study aims to analyze pharmacological interactions among drugs taken by elderly patients and their age and gender differences in a population from Porto Alegre, Brazil.

METHODS: We retrospectively analyzed the database provided by the Institute of Geriatric and Gerontology, Porto Alegre, Brazil. The database was composed of 438 elderly and includes information about the patients' disease, therapy regimens, utilized drugs. All drugs reported by the elderly patients were classified using the Anatomical Therapeutic and Chemical Classification System. The drug-drug interactions and their severity were assessed using the Micromedex® Healthcare Series.

RESULTS: Of the 438 elderly patients in the data base, 376 (85.8%) used pharmacotherapy, 274 were female, and 90.4% of females used drugs. The average number of drugs used by each individual younger than 80 years was 3.2 ± 2.6. Women younger than 80 years old used more drugs than men in the same age group whereas men older than 80 years increased their use of drugs in relation to other age groups. Therefore, 32.6% of men and 49.2% of women described at least one interaction, and 8.1% of men and 10.6% of women described four or more potential drug-drug interactions. Two-thirds of drug-drug interactions were moderate in both genders, and most of them involved angiotensin-converting enzyme inhibitor, non-steroidal anti-inflammatory, loop and thiazide diuretics, and β-blockers.

CONCLUSION: Elderly patients should be closely monitored, based on drug class, gender, age group and nutritional status.

KEYWORDS: Older Adults; Polytherapy; Pharmacology; Drug-Drug; Interaction; Hazards.

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INTRODUCTION

Aging is the main risk factor for the development of chronic diseases, and this phenomenon is increasing worldwide.[1] Although chronologic age is most often used to define the population ≥65 years old in developed countries and >60 years old in developing countries, the elderly are considered a heterogeneous group, with individuals aging at varying rates.[2]

The elderly are the predominant users of pharmaceuticals in the population.[3] Thus, aging of the population could be a reason for an increased use of pharmaceutical products. These patients often have multiple diseases, and so they require multiple drugs. It is well documented that polypharmacy has a greater potential to lead to drug interactions and adverse events.[4] Pharmacological interactions contribute to the decreased in general health in the elderly, leading to disability, reduced quality of life, raising the number of hospital admissions, a longer duration of hospital stays, a greater need for ambulatory services, and increased healthcare costs.[5]

Physiological alterations in the body with age make the elderly more susceptible to interactions. These processes include a decrease of renal function and hepatic metabolism, gastro-intestinal tract alterations, and nutritional status deficiency.[6] Therefore, body fat gains and muscle mass losses are normally seen in the elderly population, and these factors are also determinants of the intensity of drug interactions.[7]

Considering the prevalent use of polypharmacy and the health hazards due to drug-drug interaction in the elderly, this study aims to analyze potential pharmacological interactions among drugs taken by elderly patients and

No potential conflict of interest was reported.

their age and gender differences in a population from Porto Alegre, Brazil.

METHODS

This observational, cross-sectional study is part of an epidemiological project (Multidimensional Study of Elderly in Porto Alegre) that represents a partnership between the Porto Alegre City Hall and the Instituto de Geriatria e Gerontologia (IGG) - Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS). The elderly interviewed were randomly recruited, between January 2006 and May 2007, by the University social service professionals, from different socioeconomic groups as previously described by Faggiani et al.[8] To participate in this research study, the following inclusion criteria were used: individuals were able-bodied (to allow for travel to the interview site) and were older than sixty years old. The elderly who refused to participate in the study were excluded. The sample size for this study was in accordance to the number of individuals estimated for each neighborhood of Porto Alegre and was updated by the Brazilian Institute of Geography and Statistics according to an estimation of the population variation through 2005.[9]

The database generated from Multidimensional Study of Elderly in Porto Alegre was used in the present study for retrospective analysis. The database was constructed from a previously validated pharmacotherapeutic questionnaire that elderly filled out based on their memory and/or using materials supplied to them, such as prescriptions and/or a prescription label. The data were collected, and results were kept in and the individual patient's file, together with the completed questionnaires.

For the present study, we retrospectively analyzed the database provided by the IGG. To evaluate potential drug-drug interactions (DDI), we considered the most frequently interacting drug pairs in a computerized database[10] of the pharmacotherapy used in elderly individuals from Porto Alegre-RS, Brazil. The database was composed of 438 elderly and includes information about the elderly general disease and therapy regimens, the prescribed and utilized drugs, the general pharmacological classes, of those drugs, the number of drugs used, and the frequency of self-medication (all drug administration, except those prescribed by a physician).

The Anatomical Therapeutic and Chemical Classification System (ATC)[11] was used to classify the drugs that the elderly reported using, and the analysis of the potential DDI was performed according to Reis and Cassiani,[12] using the computer software Micromedex® Healthcare Series (Thomson MicromedexTM, Greenwood Village, Co, USA).[13] A severity rating scale employing the categories of ''low'' interaction (risk of adverse outcomes appears small), ''moderate'' interaction (to avoid administration unless it is determined that the benefit of co-administration outweighs the risk to the elderly), and ''severe'' interaction (to avoid administration of combination) was used to describe the potential DDI. Furthermore, it has been provided an association of the clinical consequences or adverse reactions to drugs and the characterization of the interaction mechanisms.

Polypharmacy was defined as the use of more than three drugs that have the potential to cause drug interactions and side effects.[4] The questionnaires contained no information about the timing of or beverage and/or food consumption with the drug administration. For this reason, all type of interactions we found in this study must be considered ''potential interactions.''

The Institutional Ethics Committee of PUCRS approved this study (number 0502935), and all the study participants signed consent forms.

The data were analyzed and tabulated using the computer program SPSS v17.0, and the results were presented as a percentage of the data set. Ninety-five percent confidence intervals (95% CI) were utilized to show differences in the elderly characteristics. Statistical analysis was performed considering age groups <80 and ≥ 80 years old using a Student's t test to compare the average between the two groups and a Pearson's Chi-Square test to identify the severity of the interactions. Results were expressed as mean $\pm$ sd, and a p-value <0.05 was considered significant.

RESULTS

In this study, a population of elderly individuals provided information on their use of all categories of drugs, and this information was analyzed to determine potential DDI within this population. Preliminarily, we evaluated three age groups (60 to 69, 70 to 79, and ≥ 80 years old). According to those results, we performed another statistical analysis considering only two age groups: <80 and ≥ 80 years old. In both analyses, we gathered information about whether individuals used drugs (yes/no), the number of drugs used per day (1 to 3, 4 to 6, and ≥ 7), the number of interactions (0, 1, 2, 3, and ≥ 4), and the severity of the interactions (low, moderate, and severe) (Table 1).

Use of pharmacotherapy

Of the 438 elderly individuals interviewed, 376 (85.8%) used pharmacotherapy, and only 62 (14.2%) people older than 60 years old did not use any drugs. Table 1 shows that the majority of the population (90.4%) that used drugs was female (N = 274). In this case, differences among age groups were not significant. Women <80 years old used more drugs than men in the same age group ($p<0.001$); however, in the population ≥ 80 years old, the differences between genders were not significant. Men ≥ 80 years old tended to increase their use of drugs in relation to other age groups of the same gender ($p = 0.057$). Regarding the number of drugs used by the elderly, the majority of this population used from one to three drugs (3.20 ± 2.61), and the average number of drugs used by women 79 years old or younger (3.58 ± 2.74) was higher than the average used by men (2.20 ± 2.02) in the same age group ($p<0.001$). However, among men, the number of drugs used increased with age (4.53 ± 3.23) ($p = 0.010$) (Table 1).

The majority of women (36.9%) used five or more drugs active principles, whereas the majority of men (41.2%) used between one and two drugs active principles. Among men, the number of drugs' active principles used increased with age ($p = 0.012$).

Potential drug-drug interactions

We found that the number of potential DDI increased in parallel with the number of drugs used by the elderly. In all age groups analyzed, 32.6% of men and 49.2% of women described at least one interaction. Moreover, 8.1% of men and 10.6% of women reported four or more potential DDI. Among women, the DDI were more

Table 1 - Drug use and intensity of interaction in the elderly, according to gender and age group (N = 438).

VARIABLE	TOTAL	AGE GROUP		
		<80	≥80	*p*-value
DRUG USE [N(%)]				
Men	102 (75.6)	86 (72.9)	16 (94.1)	**0.057****
Women	274 (90.4)	239 (90.9)	35 (87.5)	0.499**
p**	**<0,001**	**<0,001**	0,657	
Total	376 (85.8)	325 (85.3)	51 (89.5)	0.399**
NUMBER OF MEDICATIONS (m ± sd)				
Men	2.50 ± 2.33	2.20 ± 2.02	4.53 ± 3.26	**0.010***
Women	3.51 ± 2.67	3.58 ± 2.74	3.03 ± 2.12	0.219*
p*	**<0.001**	**<0.001**	0.094	
Total	3.20 ± 2.61	3.15 ± 2.61	3.47 ± 2.58	0.390*
NUMBER OF DRUG ACTIVE PRINCIPLES (m ± sd)				
Men	2.65 ± 2.59	2.33 ± 2.25	4.88 ± 3.64	**0.012***
Women	3.88 ± 2.99	3.97 ± 3.07	3.35 ± 2.36	0.225*
p*	**<0.001**	**<0.001**	0.124	
Total	3.50 ± 2.92	3.46 ± 2.93	3.81 ± 2.86	0.403*
NUMBER OF INTERACTIONS (m ± sd)				
Men	0.87 ± 1.89	0.71 ± 1.50	2.00 ± 3.46	0.149*
Women	1.33 ± 2.36	1.42 ± 2.49	0.73 ± 0.93	**0.001***
p*	**0.048**	**0.001**	0.153	
Total	1.19 ± 2.23	1.20 ± 2.25	1.11 ± 2.09	0.760*
INTENSITY OF INTERACTION [N(%)]				
Men				
Low	4 (9.1)	3 (8.6)	1 (11.1)	0.955**
Moderate	31 (70.5)	25 (71.4)	6 (66.7)	
Severe	9 (20.5)	7 (20.0)	2 (22.2)	
Women				
Low	13 (8.7)	9 (7.0)	4 (20.0)	0.157**
Moderate	104 (69.8)	92 (71.3)	12 (60.0)	
Severe	32 (21.5)	28 (21.7)	4 (20.0)	
p*	0.988	0.936	0.842	
Total				
Low	17 (8.8)	12 (7.3)	5 (17.2)	0.216**
Moderate	135 (69.9)	117 (71.3)	18 (62.1)	
Severe	41 (21.2)	35 (21.3)	6 (20.7)	

(m ± sd): mean ± standard deviation.
*p-values were based on Student's T-test;
**p-values were based on Pearson's Chi-Square test.

frequent in individuals younger than 80 years old ($p = 0.001$), whereas men experienced more potential DDI as age increased; most DDI in men occurred after age 80. Regarding the intensity of drug interactions, two-thirds of them were of moderate severity in both genders, and there were no statistically significant differences among all age groups analyzed.

Among those individuals who used drugs, there were 591 interactions reported. The 30 most frequent types of DDI are shown in Table 2 (intensity and possible effects), most of them involving angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril), non-steroidal anti-inflammatory (NSAIDs) agents (e.g., aspirin, diclofenac, ibuprofen), loop and thiazide diuretics (e.g., furosemide, hydrochlorothiazide), and β-adrenergic blockers (e.g., propranolol).

According to our data, cardiovascular system drugs were the most prescribed drug class (62.3%). The second most frequently used drugs were analgesic and anti-inflammatory agents (34.6%), followed by central nervous system drugs (20.8%). Unexpectedly, vitamin and mineral supplements are used by 15.1% of the patients studied.

DISCUSSION

In this study, we examined an elderly population from Porto Alegre, RS, Brazil, and analyzed drug consumption and the potential DDI as well the intensity of DDI in both genders and in several age groups of elderly patients. Other studies reporting drug utilization by the elderly from different countries have already been performed and have shown a high incidence of polytherapy.[14,15] Although there are several published studies describing polypharmacy and pharmacological interactions, such data on Brazilian patients over 80 years old are lacking. Furthermore, only a few studies have compared differences between genders in this age population.

We found that most of the elderly who use drugs are female. Although it is known that women both consult a physician more frequently and participate more often in research studies, data from the Brazilian Institute of Geography and Statistics show that female residents in Porto Alegre outnumber male residents.[9,16] Previous studies conducted in Porto Alegre, Brazil, using the elderly population have shown that the elderly use around 3.2 drugs per day and that females uses more drugs.[8,16]

As reported by Flores and Mengue,[16] the average number of medications can be higher because people do not commonly consider some agents to be drugs, such as therapies for obesity, allergy, pain, diarrhea, disorders of the kidney or bladder or digestive tract, as well nutritional (vitamins and mineral) supplements.

Table 2 - The 30 most frequent Drug-Drug Interactions (DDI) in the elderly.

Interaction	Intensity*	N (%)	Possible Effects
Verapamil - Sinvastatin	Severe	10 (1.7)	Increased risk of myopathy or rhabdomyolysis
Digoxin - Spironolactone	Severe	5 (0.9)	Digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
Captopril - Aspirin	Moderate	33 (5.7)	Decreased captopril effectiveness
Enalapril - Thiazide Diuretics	Moderate	30 (5.2)	Postural hypotension (first dose)
Captopril - Thiazide Diuretics	Moderate	25 (4.3)	Postural hypotension (first dose)
Propranolol - Hydrochlorothiazide	Moderate	25 (4.3)	Hyperglycemia, hypertriglyceridemia
Aspirin - Enalapril	Moderate	23 (3.9)	Decreased effectiveness of enalapril
Aspirin - Furosemide	Moderate	19 (3.3)	Blunting of the diuretic effect of furosemide
Enalapril - Metformin	Moderate	14 (2.4)	Hyperkalemic lactic acidosis
Aspirin - Verapamil	Moderate	14 (2.4)	Increased risk of bleeding
Aspirin - Aluminum, Calcium or Magnesium Containing Products	Moderate	12 (2.1)	Decreased salicylate effectiveness
Diclofenac - Hydrochlorothiazide	Moderate	9 (1.6)	Decreased diuretic and antihypertensive efficacy
Furosemide - Digoxin	Moderate	9 (1.6)	Digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
Captopril - Furosemide	Moderate	9 (1.6)	Postural hypotension (first dose)
Captopril – Ibuprofen	Moderate	8 (1.4)	Decreased antihypertensive and natriuretic effects
Ibuprofen - Hydrochlorothiazide	Moderate	8 (1.4)	Decreased diuretic and antihypertensive efficacy
Enalapril - Furosemide	Moderate	8 (1.4)	Postural hypotension (first dose)
Aspirin - Ibuprofen	Moderate	8 (1.4)	Decreased antiplatelet effect of aspirin
Diclofenac - Captopril	Moderate	6 (1.0)	Decreased antihypertensive and natriuretic effects
Glibenclamide - Hydrochlorothiazide	Moderate	6 (1.0)	Decreased glyburide effectiveness
Levothiroxine - Sinvastatine	Moderate	6 (1.0)	Decreased levothyroxine efficacy
Aspirin - Spironolactone	Moderate	6 (1.0)	Decreased spironolactone effectiveness
Aspirin - Diclofenac	Moderate	6 (1.0)	Reduced diclofenac efficacy
Propranolol - Nifedipine	Moderate	6 (1.0)	Hypotension and/or bradycardia.
Fluoxetine - Aspirin	Moderate	6 (1.0)	Increased risk of bleeding.
Metformin - Propranolol	Moderate	5 (0.9)	Hypoglycemia, hyperglycemia, or hypertension
Aspirin - Glibenclamide	Moderate	5 (0.9)	Increased risk for hypoglycemia
Propranolol - Furosemide	Moderate	5 (0.9)	Hypotension, bradycardia
Alendronate - Calcium ($Ca\ Co_3$)	Low	13 (2.3)	Reduced alendronate absorption
Ibuprofen - Propranolol	Low	7 (1.2)	Decreased antihypertensive effect

*__Intensity Low:__ risk of adverse outcomes appears small; __Intensity Moderate:__ to avoid administration unless it is determined that the benefit of co-administration outweighs the risk to the elderly; __Intensity Severe:__ to avoid administration of combination.

Surprisingly, after their eighties, men seem to take more drugs and drug active principles. Similarly, in this study, we found that women used more drugs than men only until the age of 79. Women are more concerned with their health and consult health services more often and earlier than men, and women are more accustomed to the use of drugs. In addition, more health programs are developed for women, such as colon and breast cancer prevention programs.[17] Furthermore, women more easily adopt the sick role; they tend to recognize and experience more health problems, more underlying gender-related psycho-social and behavioral influences, and to perceive more symptoms than men.[18,19] These factors could explain the greater use of medications by women and therefore the higher number of DDI in among women younger than 79 years old. These attitudes also provides to this group better medical monitoring and treatment of disease and early diagnosis.

For some time, geriatricians have preferred to minimize the number of drugs they prescribe to elderly patients to prevent side effects and interactions.[20] This medical management could explain the decreased use of drugs among the over-80 population, especially because recent studies have shown that inappropriate prescriptions is a great risk factor for adverse drug events and interactions in the elderly population.[21,22] Otherwise, men generally visit doctors later than women, after their disease process has already begun or when the symptoms have already presented.[19] It is important to highlight the fact that, in the south of Brazil, the life expectancy is around 81 years old,[7] and this fate can explain why men start to visit doctors later in their life.[23]

Similarly to other studies, our results show that the majority of the elderly patients in this study used cardiovascular system drugs, central nervous system drugs, and anti-inflammatory agents.[8,16] The majority of interactions was of moderate intensity and also involved cardiovascular system drugs and NSAIDs. In fact, there are DDI studies in the literature, but there is little agreement among them with respect to the severity and clinical importance of interactions.[24]

According to Schroeter et al.,[25] the majority of the elderly use the following combinations of cardiovascular drugs: a diuretic and a β-adrenergic blocker, or a diuretic, a β-adrenergic blocker, and an angiotensin-converting enzyme inhibitor (ACE). Even though diuretics are widely recommended by the World Health Organization (WHO)[26] to optimize therapeutic effects and diminish adverse events, loop and thiazide diuretics largely contribute to moderate-severity interactions, mainly when they are used with captopril, propranolol and aspirin.

These associations might result in pharmacodynamic interactions, leading to a loss of drug efficacy. For example, the use of NSAIDs in patients receiving antihypertensive therapy with β-adrenoceptor antagonists (β-blockers), thiazides, or ACE inhibitors can result in a loss of antihypertensive action.[27] In the elderly, pharmacodynamic interactions are of particular relevance because they can reduce homeostatic mechanisms, and the elderly are therefore particularly

sensitive to combined postural hypotensive or sedative effects of drugs.

In the case of aspirin, an NSAID, many interactions can occur when it is combined with other drugs. In most of them, aspirin leads to a decrease in the effectiveness of other drugs, which might result in an increase in the dosage prescribed. Otherwise, aspirin might increase the effect (or side effect) of other drugs. In both cases, co-administration with aspirin might increase the number of adverse events, which can be confused with the severity of comorbidities. The consequences of such interactions include a longer duration of hospital stays with administration of more drugs to patients, resulting in a higher probability of DDI.[28]

Another combination frequently used is digoxin and furosemide, as reported by Moura et al.[29] While in our results this pair of drugs does not represent the most frequent interaction, it is responsible for moderate-intensity interactions that might precipitate or contribute to the development of arrhythmias, especially in patients with pre-existing cardiac abnormalities. These effects can be prevented by dietary sodium restriction or by addition of potassium-sparing diuretics.[30]

We also observed in our results a few severe interactions that mainly involving the following drug combinations: verapamil and sinvastatin that are both CYP3A4 inhibitors, and their co-prescription might result in an increase in the bioavailability of the statin, with a greater risk of myopathy or rhabdomyolysis, as was well-documented by Molden et al.[31] and Jacobson;[32] digoxin and spironolactone due to this last drug reduces renal clearance and increases serum concentration of digoxin, thus its dose should be reduced in cases of combination with spironolactone.[33]

Although we could not evaluate real side effects, the computer program used in this study provided information about the associated clinical consequences or adverse reactions to drugs and characterized the interactions mechanisms. The same methodology has been previously used by others.[12,34,35]

In the last several decades, polypharmacy among the elderly has increased due to several reasons such as the increase of life expectancy, the prevalence of non-degenerative chronic diseases with complex pharmacotherapeutic regimens,[14] the introduction of new drugs to the pharmaceutical market, self-medication including herbal drugs, misuse of medication, poor quality of doctors' choices of prescriptions, doctors' over-prescription of drugs, additional medicines prescribed to treat side effects, and poor doctor-patient relationships.[3,15]

Physiological changes related to age can lead to pharmacokinetic and pharmacodynamic changes in elderly patients, and these changes seem to be more serious among women.[7] Furthermore, women take more medicines and self-report worse health than men. Older women who have more income use more prescribed drugs.[36] As Wortman et al.[37] reported, in the city of Porto Alegre, Brazil, the use of benzodiazepines is higher among older and widowed or divorced women. It is important to emphasize that female life expectancy is about 7.62 years higher than that of males in Brazil.[23]

In this study, we found that until 79 years of age, women had more interactions than men in the same age group, probably because women also use higher numbers of drugs until this age. Thereafter, it is possible that women self-medicate more often and that they do not consider several kinds of medications to be drugs.[16] Female patients have a greater risk of developing adverse drug reactions than males due to multiple pharmacokinetic parameters, such as a lower rate of drug absorption, reduced hepatic clearance, a greater percentage of body fat with age that can increase distribution volumes for lipophilic drugs, and higher oral bioavailability.[7] In the same way, gastric acid secretion, gastrointestinal and renal blood flow, and immunological differences, are several factors that might contribute to sex-related differences in pharmacokinetics.[38]

Greater body mass in men results in alterations of the distribution volume and total clearance of most medications. Besides, gender differences in oxidative metabolism, conjugation, and renal filtration; secretion, and reabsorption lead to faster drug clearance in men compared with women.[38]

There are also pharmacodynamic differences between men and women, particularly for cardiac and psychotropic medications. For instance, various antipsychotics appear more effective in women than men for the same dosage and plasma concentration. Furthermore, women are at increased risk for half-life prolongation with certain anti-arrhythmic drugs compared with men, even at equivalent serum concentrations.[7]

In order to prevent DDI or diminish its consequences, several measures should be considered for elderly patients, including periodic review of their medicines and their adverse events, preference for monotherapy as soon as possible instead of associations containing fixed dosages, choice of drugs with proven efficacy, and suspension of drug use as soon as possible. Therefore, the comprehensiveness of the prescriptions and the pharmacologic orientations beyond simply the regimen should be evaluated.[39]

For reducing drug-drug and food-drug interactions, it might also be important to change the administration schedule for elderly patients at risk for nutritional deficiency.[6] This practice aims to diminish potential adverse drug reactions and prevent aggravation of the clinical features that occurs due to the great number of drugs utilized by each elderly individual.

The present study demonstrates that potential drug interactions in the elderly correlate with the concomitant use of multiple drugs. Furthermore, elderly patients should be closely monitored for adverse drug reactions and potential pharmacological interactions, particularly with drugs that target the cardiovascular system, given our finding that they were the most commonly used class of drug and the most frequently involved in drug interactions.

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AUTHOR CONTRIBUTIONS

Venturini CD, Engroff P, Ely LS were responsible for the study's methodology, data interpretation and final writing of the paper. Zago LFA, Schroeter G and Gomes I were responsible for the study's methodology and data interpretation. De Carli GA and Morrone FB were responsible for the preparation and design of the study, final writing, and correction of the paper.

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