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Article

Potential interactions of central nervous system drugs used in the elderly population

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Objective: To describe the use of CNS drugs and to identify the most frequently observed potential drug interactions in the elderly living in Southern Brazil. Methods: A population-based, transversal and observational study was carried out during 2006-2007. Four hundred and eighty elderly individuals of both genders were randomly recruited and interviewed. A validated pharmacotherapeutic questionnaire and the Micromedex® Healthcare Series were utilized to analyze potential drug interactions. A severity rating scale employing the categories of "mild", "moderate" and "severe" was used to describe the interactions. Results: A population of elderly living in Southern Brazil was interviewed and 98 reported using CNS drugs, 74.5% female and 25.5% male. Out of these patients, 32.0% reported severe or moderate pharmacological interactions related to the use of other drugs. Alprazolam and imipramine were reported to potentially interact with tobacco. Twenty potential moderate drug/ethanol interactions were found. The potential drug/caffeine interactions were classified as mild on the severity scale. Conclusion: Elderly being prescribed drugs that act on the CNS should be closely monitored, and furthermore, should be warned against potential drug-drug, drug-ethanol, and drug-tobacco interactions.

Uniterms: Elderly. Drug-Drug interactions. Central nervous system. Tobacco. Ethanol.

Objetivo: Descrever o uso de medicamentos que atuam no sistema nervoso central (SNC) e identificar as possíveis interações mais frequentes com esses medicamentos em idosos do sul do Brasil. Métodos: Estudo de base populacional, transversal e observacional, realizado durante 2006-2007. Quatrocentos e oitenta idosos de ambos os sexos foram randomizados e entrevistados. Foram utilizados um questionário farmacoterapêutico validado e o programa Micromedex® Healthcare Series para analisar as potenciais interações com os medicamentos. Foi utilizada uma escala para descrever a gravidade das interações nas categorias de "leve", "moderada" e "grave". Resultados: A população idosa, moradora do sul do Brasil, que utilizava medicamentos para o SNC, era formada por 98 pacientes, 75,5% mulheres e 25,5% homens. Destes pacientes, 32,0% apresentaram interações farmacológicas graves ou moderadas relacionadas com a utilização de outros medicamentos. Alprazolam e Imipramina, usados pela população, apresentaram riscos de potenciais interações com tabaco. Foram encontradas vinte potenciais interações moderadas medicamento/etanol. As potenciais interações medicamento/cafeína foram classificadas como leves. Conclusão: Os pacientes idosos deveriam ser rigorosamente monitorizados, e ainda, é necessário advertir quanto às potenciais interações de medicamentos que atuam no SNC com outros medicamentos, etanol e tabaco.

Unitermos: Idosos. Interações medicamento-medicamento. Sistema nervoso central. Tabaco. Etanol.

INTRODUCTION

The mean age of the world's population is increasing and this phenomenon is leading to increased demands on the public health system and on medical and social services. The increased proportion of older adults has raised the number of hospital admissions, leading to longer hospital stays and a greater need for ambulatory services (Nordberg *et al*., 2007).

Aging is a major risk factor for chronic diseases

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(Chen, Dewey, Avery, 2001) and the enlarged elderly population increases the prevalence of many central nervous system (CNS) disorders, such as Alzheimer disease, stroke, and Parkinson's disease, as well as depression, anxiety, and insomnia. Such disorders affect older adults disproportionately, and contribute to disability, a decreased quality of life, and increased healthcare costs.

The elderly are the predominant users of pharmaceuticals in the population and inappropriate prescribing of medication is a concern since it increases the risk of drug-related problems (Paulino *et al.*, 2004). Additionally, elderly patients often require multiple drugs and it is well documented that polypharmacy has a greater potential to lead to drug interactions and adverse events (Evans *et al.*, 2003; Frankfort *et al.*, 2006). Furthermore, because of age-related changes in pharmacodynamic and pharmacokinetic parameters, elderly patients are more likely to experience adverse effects from CNS agents than younger patients (Mort, Aparasu, 2002).

In this regard, physiological changes, such as decreased renal function and hepatic metabolism and mental impairment make the elderly more vulnerable to drug-related problems (Woodhouse *et al*., 1988). Many other factors can also contribute to changes in the drug response, such as the complexity of the brain, the liability of CNS drugs to cause side effects, and the requirement of CNS drugs to cross the blood-brain barrier (Higashi *et al.*, 2004).

Drug interactions, such as drug-drug, drug-food, and drug-tobacco are considered another important risk factor for health problems in elderly (Keegan, Brown, Rabinstein, 2006). Recently published studies have demonstrated that the use of drugs, polypharmacy and potential drug-drug interactions (DDIs) have increased during the last several years among patients, representing potential health hazards for the elderly (Astrand *et al.*, 2007; Haider *et al.*, 2007; Johnell, Klarin, 2007). According to these studies, there seems to be a strong relationship between the number of dispensed drugs and potentially serious DDIs, and the pronounced increase in polypharmacy over time serves as an excellent reason for prescribers and pharmacists to be aware of drug interactions (Astrand *et al.*, 2007; Johnell, Klarin, 2007).

Considering the prevalent use of psychotropic medications in elderly patients, this study aims to describe the use of CNS drugs and to identify the potential drug interactions most frequently observed in elderly living in Southern Brazil.

METHODS

A population-based, transversal and observational study was carried out during the months of January 2006 until May 2007. A qualitative and quantitative drug utilization study was also performed.

The elderly interviewed were randomly recruited, by the University social service professionals, from different socioeconomic groups as previously described by Faggiani *et al*., 2007. Briefly, Porto Alegre City Hall provided the data for different neighborhoods where elderly citizens are concentrated within the population, as well as the names and addresses of these individuals. The sample size for this study was similar to the number of elderly analyzed in a previously published study (Rio Grande do Sul, 1996) for each neighborhood of Porto Alegre and was updated according to an estimate of the population variation through 2005 developed by the Instituto Brasileiro de Geografia e Estatística - IBGE (IBGE, 2003). Four hundred and eighty elderly individuals of both genders were interviewed. For the sample size calculation, it was assumed a percentage of 0.69% to obtain a confidence interval of 99%.

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.

Trained interviewers conducted the interviews. A previously validated pharmacotherapeutic questionnaire containing the patient's general lifestyle information (age, habits and alcohol intake), disease, therapy regimens and information about the prescribed and utilized drugs was used to document the responses. The questions were open-ended and were answered based on the memory of the patient and/or using materials supplied to the patient, such as prescriptions and/or a label.

The Anatomical Therapeutic and Chemical Classification System (ATC) (WHO, 2004) was used to classify the drugs that the elderly reported using and the Micromedex® Healthcare Series was used to analyze the interactions (Klasco, 2005). A severity rating scale employing the categories of "mild" 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 patient), and "severe" interaction (to avoid administration of combination) was used to describe the potential drug interactions.

After the data were collected, the results were kept in the individual's patient file together with the completed questionnaires. The data were analyzed and tabulated using the computer program, SPSS version 11.5, and the results were presented as a percentage of the data set. Ninety-five percent confidence intervals (95% CI) were utilized to show difference in the patient's characteristics (Zar, 1999).

The PUCRS Institutional Ethics Committee approved this study (protocol number 0502935) and the study participants signed the consent form.

RESULTS

In this study, a population of elderly individuals provided information on their use of central nervous system drugs, and these informational data were analyzed to determine potential drug interactions that were being experienced within this population. Out of the 480 elderly interviewed, 64.0% used cardiovascular system drugs, 35.0% used analgesic/anti-inflammatory drugs, and 20.5% of the elderly used drugs that predominantly act on the CNS.

Preliminarily, we gathered general information and lifestyle habits of the population. Table I shows that the majority of elderly population who used CNS drugs were female (74.5%). The mean age of the population was 72.0 (SD=6.3) for men and 73.5 (SD=6.5) for women and the average number of medications used by each patient was 2.6 (SD=2.2) for men and 3.8 (SD=2.6) for women. According to our data, elderly men consumed more alcohol (56.0%) and tobacco (24.0 %) than women did. These results lead us to also investigate the potential interactions of the prescribed CNS drugs with ethanol and/or tobacco use.

TABLE I - Characteristics of the elderly population using CNS acting drugs (n=98)

	Men		Women	
	n=25 [25.5%]	[95%CI]	n=73 [74.5%]	[95%CI]
Age average	72.6 ± 6.3		73.5 ± 6.5	
Drugs average	2.6 ± 2.2		3.8 ± 2.6	
Tobacco use	n=6 [24.0%]	[9.4 - 45.1]	n=10 [13.7%]	[6.8 - 23.8]
Ethanol use	n=14 [56.0%]	[34.9 - 75.6]	n=20 [27.4%]	[17.6 - 39.1]

CI = confidence interval

Figure 1A shows the predominant psychiatric pathologies diagnosed among the studied population.

In our elderly sample population (480), 20.5% used a total of 146 CNS drugs. Amongst these, the most used were antidepressants, followed by anxiolytic/hypnotic, anticonvulsant/antiepileptic and antipsychotic/neuroleptic (Figure 1B).

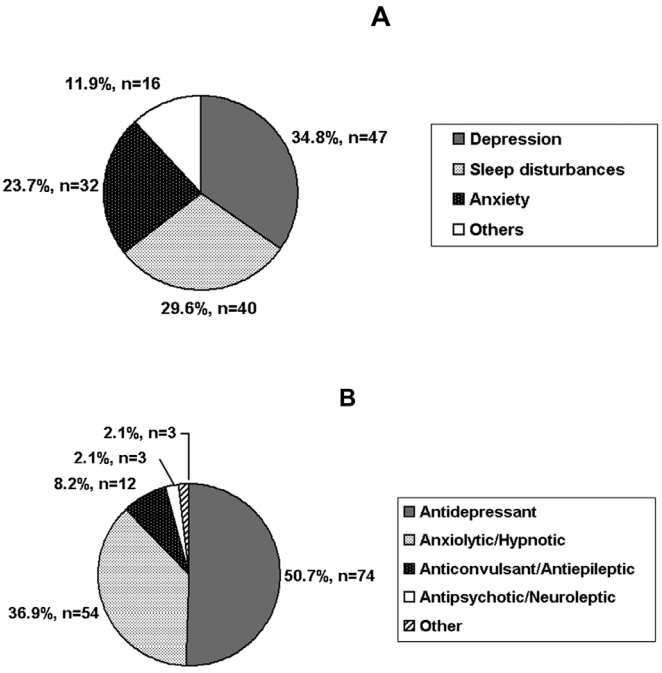

FIGURE 1 - The predominant central nervous system diseases diagnosed and reported* in the elderly sample population (n=135) **(A).** Pharmacological classes of drugs acting in the CNS, used by the elderly sample population (n=146) **(B). *** Each patient may present with more than one disease and use more than one drug.

Given that many elderly patients were prescribed and used CNS-acting drugs, we next wanted to evaluate in-depth any potential pharmacological interactions of the CNS drugs these patients could be experiencing. We found 125 potential drug interactions. These interactions predominantly occurred between drug-drug, drug-ethanol, and drug–tobacco, but we also investigated drug-caffeine interactions, since some of the interviewed population typically took their medications with coffee.

As reported at Table II, we determined that 40 (32.0%) of the potential DDIs were either severe or moderate on the severity scale. Among these, we identified the contraindication for use of amitriptyline and tranylcypromine (parnate®) in one patient, which can lead to neurotoxicity and serotonin syndrome. We found five severe drug interactions, most of them related to the use of amitriptyline together with other CNS drugs, leading to severe effects such as cardiotoxicity, tricyclic antidepressant toxicity, respiratory depression and, in some cases, a subtherapeutic effect. The other drug interactions reported at Table II are considered of moderate severity, which lead to an increased risk of psychomotor impairment and sedation, psychomotor deficits, increased risk of bleeding, and peripheral ischemia, among others. The minor interactions

TABLE II - Potential drug-drug interactions, based on reported prescribed medications in the elderly sample population of (n=40)

Interaction	Intensity	Possible effects	n (%)
Tranylcypromine - Amitriptyline	Contraindicated	Neurotoxicity, seizures, or serotonin syndrome	1 (2.5)
Amitriptyline - Clonidine	Severe	Subtherapeutical effect	1 (2.5)
Amitriptyline – Haloperidol	Severe		
Amitriptyline - Sotalol Hydrochloride		Cardiotoxicity effect	2 (5.0)
Amitriptyline - Fluoxetine	Severe	Tricyclic antidepressant toxicity and an increased risk of cardiotoxicity	2 (5.0)
Primidone - Flunitrazepam	Severe	Additive respiratory depression	1 (2.5)
Fluoxetine - Aspirin			
Fluoxetine - Diclofenac			
Fluoxetine - Ibuprofen			
Sertraline - Aspirin			
Sertraline - Diclofenac	Severe	Increased risk of bleeding	11 (27.5)
Alprazolam - Cimetidine		Toxicity	
Alprazolam - Fluoxetine		Increased risk of alprazolam toxicity	
Alprazolam - Imipramine		Increased imipramine plasma concentrations	
Alprazolam - Omeprazol		Benzodiazepine toxicity	
Amitriptyline - Cimetidine		Amitriptyline toxicity	
Fluoxetine - Metoprolol		Increased risk of metoprolol adverse effects	
Midazolam Maleate - Omeprazol		Benzodiazepine toxicity	
Phenytoin - Omeprazol		Increased risk of phenytoin toxicity	
Sertraline - Carbamazepine		Increased risk of carbamazepine toxicity	
Valproate Sodium - Aspirin	Moderate	Increased free valproic acid concentrations	12 (30.0)
Sertraline - Alprazolam	Moderate	Increased risk of psychomotor impairment and sedation	1 (2.5)
Phenytoin - Simvastatin	Moderate	Loss of simvastatin efficacy	1 (2.5)
Carbamazepine - Simvastatin	Moderate	Reduced simvastatin exposure	1 (2.5)
Carbamazepine - Phenobarbital	Moderate	Subtherapeutical effect	1 (2.5)
Sertraline - β-Blockers	Moderate	Increased risk of chest pain	1 (2.5)
Tranylcypromine - Metformin	Moderate	Excessive hypoglycemia, CNS depression, and seizures	1 (2.5)
Flunarizine - β-Blockers	Moderate	Hypotension, bradycardia, and AV conduction disturbances	1 (2.5)
Amitriptyline - Diazepam	Moderate	Psychomotor deficits	1 (2.5)
Ergotamine Tartrate - β-Blockers	Moderate	Peripheral ischemia	1 (2.5)
Carbamazepine - Hydrochlorothiazide	Moderate	Hyponatremia	1 (2.5)

TABLE III - Potential ethanol-drug interactions, based on reported prescribed medications and regular alcohol use in the elderly sample population (n=20)

Interaction (Drug + Ethanol)	Possible effects	Intensity	n (%)
Alprazolam Chlordiazepoxide Diazepam Flunitrazepam Lorazepam	Increased sedation	Moderate	13 (65.0)
Amitriptyline	Enhanced CNS depression and impairment of motor skills	Moderate	3 (15.0)
Phenytoin	Decreased phenytoin serum concentrations, increased seizure potential, and additive CNS depressant effects	Moderate	1 (5.0)
Sertraline	Increased risk of impairment of mental and motor skills	Moderate	1 (5.0)
Imipramine Chlomipramine	Enhanced drowsiness; impairment of motor skills.	Moderate	2 (10.0)

represented 12 (9.6%) and were not of clinical importance.

Regarding the regular consumption of ethanol with CNS drugs in the elderly, we identified twenty potentially moderate drug-ethanol interactions among those individuals who consume alcohol, resulting in symptoms of enhanced depression and sedation and impairment of motor skills. These interactions occurred mainly with benzodiazepines and tricyclic antidepressants (Table III).

Although many elderly smoke tobacco or have smoked it in the past, only two of the drugs used within the population, alprazolam and imipramine, presented risks of interaction with tobacco, which may decrease serum concentrations of the CNS drugs. We found that 8 (6.4%) of the reported CNS-acting drugs could interact with caffeine, but all of these potential interactions were classified as having minor severity, as caffeine use could only reduce the sedative and the anxiolytic effects of the drugs.

DISCUSSION

In the last several decades, the use of psychotropic drugs has increased in many countries. This increase has been attributed to an increase in the diagnosis of psychiatric disorders within the population, the introduction of new drugs on the pharmaceutical market, and to new therapeutic indications for the already existing CNS drugs (Barg *et al.*, 2006).

Similarly to other previously published studies, the majority of interviewed elderly who use CNS-acting drugs were female, possibly due to the fact that CNS drug use is higher amongst women simply because women more often seek help from the health services. In addition, according to the Institute of Brazilian Geography and Statistics (IBGE), the women living in Porto Alegre outnumber the men (Coelho, Marcopito, Castelo, 2004; Flores, Mengue, 2005; IBGE, 2003). On the other hand, men reported more alcohol and tobacco use than women (Table I).

In addition to the pharmacokinetic and pharmacodynamic peculiarities of drug in elderly patients, the high cost of taken drugs coupled with the fact that elderly patients are often prescribed several drugs for their various medical conditions, and it can lead some patients to take fewer drugs than their prescribed treatment regimen. On the other hand, it is also common to find that medical professionals have prescribed the elderly with inadequate dosage, incorrect indications, potential drug interactions and/or unsuitable associations, and little or no therapeutic value medications (Liu, Christensen, 2002).

According to our survey, drugs that act in the CNS for diseases such as depression, sleep-disturbances and anxiety were commonly prescribed in our sample population (Figure 1A). Around half (50.7%) of the elderly we interviewed were taking anxiolytic/hypnotics, the most commonly-prescribed drug in our sample population of CNS drug users. International guidelines suggest that benzodiazepines should not be used uninterruptedly for more than two to four weeks, and that a stoppage interval at the end of this period should be applied, before administration restarting . The use of these drugs for long periods of time can induce potentially dangerous side-effects, such as falls, memory disease and accidents (Barg *et al*., 2006).

Respecting to the potentially severe DDIs, the contraindicated use of amitriptyline-tranylcypromine was identified, which can result in serious consequences

(Table II) including neurotoxicity that can produce a poisonous or lethal effect on the nervous system. Frequently, neurological complications are also observed, such as mental alterations, cerebral ataxia, convulsions, and peripheral neuropathies. It is surprising to find that tranylcypromine prescriptions, at least in our sample population, are not being more carefully given and folowed-up for the treatment of psychiatric ailments.

Serotonin syndrome, characterized by symptoms of hallucination, muscle rigidity, lethargy, hypotension, tachycardia, and respiratory insufficiency, is another serious adverse reaction reported with serotoninergic drug use. Thus, when amitriptyline and tranylcypromine are co-prescribed, adverse events must be closely monitored, particularly in elderly patients (Araujo, Nery-Fernandes, Quarantini; 2006; Karunatilake, Buckley, 2006; Kozian, 2005; Mackay, Dunn, Mann, 1999).

Studies from different countries have been published reporting a pronounced increase in polypharmacy as patients age, which highlights the need for prescribers and pharmacists to be aware of drug interactions, particularly in elderly (Astrand *et al.,* 2007; Johnell, Klarin, 2007; Kotirum S *et al.,* 2007; Thijs *et al*., 2006). It has been estimated that patients taking two drugs face a 13% risk of drug interactions, rising to 38% when taking four drugs, and to 82% if seven or more drugs are given simultaneously (Goldberg *et al.,* 1996). Furthermore, prescription of potentially inappropriate medications to older people is highly prevalent in the United States and Europe, and inappropriate prescribing is associated with increased risk for adverse drug events (Gallagher, Barry, O'Mahony, 2007).

As previously described in several studies, other commonly-used drugs such as fluoxetine, alprazolam, and sertraline can lead to interactions of a severe or moderate intensity. The effects of these drug interactions can bring serious consequences within a short period of time and serious cases of toxicity can appear, leading to additional health problems in the elderly population (Coelho, Marcopito, Castelo, 2004).

In this study, we identified 20 moderate drug-ethanol interactions, which can result in decreased drug serum concentrations, increased seizure potential, and additive CNS depressant effects; therefore, patients who are prescribed ethanol-interacting drugs should be more strongly dissuaded from ethanol use by their physicians and pharmacists. Ethanol can interact, pharmacokinetically and pharmacologically with some CNS drugs and, in many cases, can increase their action, because both use the liver as metabolic tract. Alternatively, ethanol can suppress the action of other CNS medications because it competes with the drugs. Ethanol is a central nervous system depressant that potentiates gamma-aminobutyric acid (GABA) action and, at the same time, inhibits the glutamate action in N-methyl-D-aspartate (NMDA) receptors, causing sleepiness, irritability, and/or euphoria. Acute ingestion of ethanol in patients taking phenytoin reduces its breakdown because both drugs compete in the metabolic system. The concomitant ingestion of alcohol with paroxetine can have additive effects, such as sedation and alteration of motor abilities (Linnoila, Mattila, Kitchell, 1979).

Only two drugs, alprazolam and imipramine, were identified as interacting with tobacco; such interaction results in the reduction of both drugs concentration. Studies regarding this interaction have shown that the liberation of a number of substances (carbon monoxide, hydrogen cyanide, aldehydes, benzopyrenes, nicotine, pesticides, and nitrosamines) from tobacco used in cigarette form, can lead to a number of pharmacodynamic and pharmacokinetic interactions. Thus, some drugs have their effects diminished due to the hepatic metabolism induced by tobacco (Balbani, Montovani, 2005; Ferigolo *et al.*, 2004).

Few studies are published regarding the implications of alcohol and tobacco use and food consumption together with drug therapy. The interactions with alcohol or tobacco may be unavoidable in certain cases, since the patients may not want to quit drinking and/or smoking; however, alcohol and tobacco-interacting drugs should be prescribed with caution, if no better alternative therapy is available for the patient's disease. It is important to highlight that the need for clinical information, which should be provided and interpreted by the prescribing physician and pharmacist, is essential for the elderly patients.

Out of the potential drug/caffeine interactions observed in this study, all were potentially minor as they reduce anxiolytic and sedative effects. Caffeine is an alkali CNS stimulant that is naturally present in some plants and belongs to the group of methyl-xantines. When managed separately, it does not have significant analgesic activity; however, when taken in association with other drugs, significant consequences may occur. Caffeine opposes the hypnotic and sedative effects of barbiturates, inducing an increased necessity for these drugs, which in turn facilitates dependency (Alavijeh *et al.*, 2005).

CONCLUSION

The results presented in this study demonstrate that the risk of potential drug interactions was strongly correlated with the concomitant use of multiple drugs, alcohol and tobacco among the elderly population taking psychotropic medications. Elderly patients should be better educated by

the physician on potential interactions with prescription drugs that are commonly involved in 'severe` drug-drug, drug-ethanol, drug-tobacco, and drug-caffeine interactions, and prescribed drug combinations should be further analyzed by a clinical pharmacist prior to drug dispensing. Furthermore, elderly patients should be closely monitored for adverse drug reactions and potential pharmacological interactions, particularly with drugs that act in the CNS.

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