

## Safety Assessment of Potentially Inappropriate Medications (PIM) use in Older People and the Factors Associated with Hospital Admission

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**ABSTRACT** - Purpose: Potentially Inappropriate Medications (PIM) use in elderly people may be responsible for the development of Adverse Drug Reaction (ADR) which, when severe, leads to hospital admissions. Objectives: to estimate the prevalence of elderly who had used PIM before being admitted to hospital and to identify the risk factors and the hospitalizations related to ADR arising from PIM. Methods: A descriptive and cross-sectional study was performed in the internal medicine ward of a teaching hospital (Brazil), in 2008. With the aid of a validated form, patients aged  $\geq 60$  years, with length of hospital stay  $\geq 24$  hours, were interviewed about drugs taken prior to the hospital admission and the complaints/reasons for hospitalization. Results: 19.1% (59/308) of older patients had taken PIM before hospital admission and in 4.9%; there were a causal relation between the PIM taken and the complaint reported. PIM responsible for admissions were: amiodarone, amitriptyline, cimetidine, clonidine, diazepam, digoxin, estrogen, fluoxetine, lorazepam, short-acting nifedipine and propranolol. 47.0% of the clinical manifestations of PIM-related ADR were: dizziness, fatigue, digoxin toxicity and erythema. Only polypharmacy was detected as a risk factor for the occurrence of ADR of PIM ( $p = 0.02$ ). Conclusion: PIM use in elderly people is not a risk factor for ADR-related hospital admission. Probably, severe ADR, which lead to hospitalizations of older people, can be explained by idiosyncratic response or the predisposition of these patients to develop adverse drug events, whether or not drugs are classed as PIM.

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### INTRODUCTION

Aging of the population is a global reality. In 2050, there will be two billion people over 60 years old in the world. However, 80% of these people will be distributed among developing nations [1].

The aging process is characterized by physiological changes, which can increase the response to both therapeutic and adverse effects of drugs [2]. The main alterations, according to Corsonello et al. (2010) [3] are: reduction of hepatic clearance, glomerular filtration capacity, muscular mass, and homeostatic mechanisms. These changes can affect the pharmacokinetics and pharmacodynamics. Thus, the selection and prescription of drugs for this population must be done with particular care [4].

Therefore, some drugs are considered potentially inappropriate for older people. Potentially inappropriate medication (PIM) are those medications or classes of medications that should be avoided in patients aged  $\geq 65$  years, since they have no clear evidence-based

indication, are not cost-effective [5], pose unnecessarily high risk for older persons [6], once the risks of using overcome the benefits [7], and safer alternatives are available [6,8].

The exposure of older people to PIM is associated with the increased use of health care services [9], ADR [4,10] and higher medical costs [11]. However, PIM prescriptions are common among these patients [12], since studies have shown that 24.5% to 66.0% [8,11-16] of older people take these drugs.

One way to identify the prescription of PIM is the use validated screening tools that incorporate explicit prescribing indicators [17], such as the Medication Appropriateness Index, the criteria of McLeod and Beers and the Stopp (Screening Tool of Older Persons' potentially inappropriate Prescriptions) methods.

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However, the Beers list is most often used to evaluate the quality of prescriptions for senior citizens<sup>[17]</sup>, because it is the best known in the literature<sup>[5]</sup>.

In Brazil, several studies about PIM use in older people have been carried out, however only one evaluated hospital admissions owing to ADR to PIM<sup>[15]</sup>. Thus, due to lack of investigations on pharmacovigilance in our country, the main objectives of the present study were to: estimate the prevalence of hospitalizations of elderly related to ADR to PIM and identify risk factors associated with hospital admission of older people who had taken PIM.

## METHODS

A descriptive and cross-sectional study was performed in a public teaching hospital (848 beds), which is regarded as a reference for complex treatments by 26 cities of the state of São Paulo, Brazil, covering for a population of approximately 4,000,000 inhabitants.

All patients  $\geq 60$  years admitted to the internal medicine ward (107 beds), in the period August to December 2008, with length of stay  $\geq 24$  hours, who had used at least one drug before hospitalization and who agree to participate, signing the Informed Written Consent, were considered eligible for the study. Exclusion criteria were patients: transferred from another hospital or ward (these patients were not enrolled in the research, because if their complaints/reasons were a suspicion of adverse drug event, it would be hard to identify if this problem (ADE) was related to drugs taken prior to hospital admission or during the previous hospitalization in other hospital or ward), with pre-scheduled surgery, unable to communicate (intubated, in isolation, mentally disoriented), and those who did not want to participate.

A validated instrument (form)<sup>[15,18]</sup> was adapted for data collection, which include information about: patient identity (hospital registration, bed, date and time of hospital admission and discharge); personal history of drug treatment (to identify the drugs administered and complaints/reasons for hospitalization); questions about temporal relationship between using the drug and the appearance of effects, withdrawal and re-exposure to the drug suspected and alternative causes that could explain the case, as well as socio-demographic characteristics of older patients [alcohol consumption, smoking habits and their age group - (I: 60-64 years, II: 65-74 years, III: 75-84 years and III:  $\geq 85$  years)].

Older people were divided in for groups, since in developing countries, population aged  $\geq 60$  years are considered elderly. Therefore, patients included in group I are contemplated in specific statutes and national programs, in order to ensure their health care. Thus, this age group was enrolled in the study to estimate the prevalence of medication errors that Brazilian elderly patients could be exposed, such as PIM prescription.

Modifications made in validated form were the inclusions of the variables alcohol consumption and smoking habits (to verify whether they are detected as risk factors for occurrence of ADR) and the ADR Probability Scale<sup>[19]</sup>. The adapted form was validated during the first week of data collection in the internal medicine ward of the hospital studied. During this period, the patients were interviewed about all parameters contemplated in the form. For those patients who had an adverse event considered a suspect of ADR, the causality analysis was performed applying the ADR Probability Scale. There was no need for changes of the information contained in the instrument developed, once the questions elaborated were not ambiguous and allowed objective answers, as well as it was possible to use the ADR Probability Scale for detect adverse effects related to hospital admissions. Furthermore, the interview lasted no more than 15 minutes, allowing the patients reply the issues solicited.

The investigator made three attempts to recruit patients for the study. Subjects were interviewed about drugs taken prior to hospital admission and complaints/reasons for hospitalization. Whether patient had not brought his medical prescription to the hospital and if he mentioned that could be able to remember all drugs, the information requested depended on their memory or/and their caregivers (that were often their family member). In such cases, the medical records were not consulted, because there is a lack of information about personal history of drug treatment performed at home, once these data are generally not registered in medical records. However, when the investigator asked for the patient what drugs he had taken prior to hospital admission and the patient mentioned that he did not remember any drug taken and the medical prescription of the medication used at home was no available, the medical records were consulted as a last source of data of drugs administered.

The drugs were divided according to the Beers list<sup>[6]</sup> in two criteria (I = Criteria for PIM use in older adults: independent of diagnoses or conditions; II = Criteria for PIM use in older

adults: considering diagnoses or conditions) [6]. Criteria I contains 48 individual medications or classes of medications to avoid in older adults and Criteria II lists 20 diseases or conditions and medications to be avoided in older adults with these conditions [6]. The complaints/reasons for hospitalization considered to be ADR to PIM were classified according to ICD-10 and the ADR Probability Scale (APS), developed by Naranjo et al (1981) [19].

The labeling approved by the National Agency of Sanitary Surveillance (ANVISA), monographs on the drug, such as DRUGDEX (database MICROMEDEX ®), and scientific papers were used as the basis of information on the drugs. More than one source of information of drugs was used, once the labels of drugs approved by ANVISA describe the ADR that occur with more frequency, whose occurrences are more probable, and those considered severe (e.g., idiosyncratic reactions). Therefore, whether other literature had not been consulted, the prevalence of hospital admission related to ADR to PIM could be underestimated. However, for all drugs reported by elderly people, the same sources of information were consulted.

ADR was defined any response to a drug which is noxious and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis or therapy of disease or for the modification or physiological function [20]. Polypharmacy was considered the concomitant use of five or more drugs [21].

Descriptive statistics were applied to PIM use and its related ADR, showing them in terms of frequency. The odds ratio (OR) was calculated for the variables gender, ethanol consumption and smoking habits. The chi-squared test was applied to assess the association between age groups and hospitalization due to PIM use and ADR to PIM. Mann-Whitney test was used to assess statistical difference among patients admitted due to ADR to PIM and patients without ADR identified, in relation to the variables number of and length of stay. A p value < 0.05 was regarded as indicating significance. The study protocol received the ethical approval of the Ethics Committee of the hospital under study.

## RESULTS

### *Prevalence of ADR related to hospital admission:*

During the study period, 1,180 patients were admitted to the internal medicine ward, of whom 308 contemplated the inclusion criteria. Of these,

168 could not be interviewed, since they were in a medical consultation, conducting surveys or asleep (after three attempts to recruit them); four denied consuming any drugs, seven did not know what drugs they had taken (the personal history of drug treatment performed at home was not registered in medical records), and 129 had used at least one drug before hospitalization, among whom 59 (19.1%) reported taking PIM.

ADR related hospital admissions were identified in 60 patients, of which 27 had taken PIM. However, the use of these drugs was responsible or/and co-responsible for the hospitalization of 15 [4.9% (15/308)] older people admitted to the ward under study. The other 12 patients, even using PIM, the ADR were caused by drugs not covered by the list of Beers.

### *Analysis of the causality of ADR:*

Older people reported 167 different drugs, of which 58 were responsible for 99 ADR. Of these ADR, 4 were related to the use of PIM [digoxin toxicity (2), erythema (1) and breathlessness (1)], 82 to the use of drugs other than PIM and 13 of both categories of drugs (PIM and non PIM). The majority (57.6%) of ADRs identified were classified as "possible", according to the APS [19].

### *Socio-demographic profile of patients admitted due to ADR to PIM and risk factors for hospitalization:*

Regarding age groups, 30 older patients belonged to group I, 55 to the group II, 39 to group III and five to group IV. Of these elderly, 13, 22, 22 and 2 reported PIM use, respectively. To calculate the chi-squared, a contingency table 3x2 was drawn up. Patients with age among 60-74 years (group I and group II) comprised one group for the calculus, since Brazilian elderly aged  $\geq 60$  years old. However, there was no statistically significant difference between age groups in use of PIM ( $p = 0.25$ ). Chi-squared test also did not show association between patients who had their hospitalization related to PIM use and age groups ( $p=0.99$ ). Therefore, there is no evidence that patients with advanced age (who belong to groups III and IV) are more susceptible to be admitted in hospital due to ADR of PIM.

The Mann-Whitney test indicated significant differences for the variables polypharmacy and length of stay, since there is evidence that patients hospitalized because of ADR to PIM were taking a larger number of drugs before admission ( $p = 0.02$ ) and stayed less time in hospital ( $p = 0.04$ ) than patients admitted for other reasons.

**Drugs related to hospital admission:**

Of the 167 drugs reported, 20 (12.0%) were considered PIM for older people (Table 2). Most of the patients who reported PIM [93.2% (55/59)] had taken PIM that belonged to criteria I, 3 older people had taken PIM that belonged to criteria II and 1 had taken PIM of both criteria.

The drug-disease interactions observed were: chronic obstructive pulmonary disease with nonselective  $\beta$ -blockers (propranolol), blood-clotting disorders with acetylsalicylic acid and syncope with clonazepam (Table 2).

Of the PIM reported, 11 (55.0%) were related to complaints / reason for hospitalization. The PIMs responsible for hospital admission were:

amitriptyline, digoxin and propranolol. Those co-responsible were: amiodarone, amitriptyline, cimetidine, clonidine, diazepam, digoxin (dose above 0.125 mg / d), estrogen, fluoxetine, lorazepam (dose above 3 mg) and short-acting nifedipine. However, the use of PIM was not detected as a risk factor for occurrence of ADR [OR = 1.0, 95% CI (0.5 to 2.1)].

ADR related to use of these drugs, according to ICD-10, were: symptoms, signs and abnormal clinical and laboratory findings not classified elsewhere, disorders in the digestive, respiratory and circulatory tracts, in the skin and subcutaneous tissue and external causes (Table 3).

**Table1.** Frequency of Adverse Drug Reactions of potentially inappropriate medication, according to gender of patients, alcohol consumption and smoking habits (n=129)

Variable	ADR		OR	(IC95%)	p
	n	n			
<i>Gender</i>					
Female	31	9	0.6	(0.2-2.1)	0.53
Male	13	6			
<i>Alcohol consumption</i>					
Yes	5	1	0.5	(0.06-5.2)	1.00
No	39	14			
<i>Smoking habits</i>					
Yes	3	1	1.0	(0.1-10.2)	1.00
No	41	14			

**Table2.** Potentially inappropriate medication as determined by Beers' list, categorized into criteria I and II (n=78)

Criteria I	n (%)	Criteria II	n (%)
digoxin (dose should not exceed > 0.125 mg/d except when treating atrial arrhythmias)	19 (26.0)	clonazepam	2 (50.0)
amiodarone	8 (11.0)	acetylsalicylic acid	1 (25.0)
ferrous sulfate (doses greater than 325mg/d)	8 (11.0)	propranolol	1 (25.0)
clonidine	7 (9.0)		
fluoxetine (daily)	7(9.0)		
amitriptyline	4 (5.0)		
diazepam	4 (5.0)		
nifedipine (short-action)	4(5.0)		
ticlopidine	3 (4.0)		
cimetidine	2 (3.0)		
mineral oil	2 (3.0)		
dexchlorpheniramine	1 (1.0)		
estrogen	1(1.0)		
lorazepam (doses greater than 3mg)	1(1.0)		
methyldopa	1(1.0)		
nitrofurantoin	1(1.0)		
promethazine	1(1.0)		
<b>Total</b>			<b>78</b>

**Table3.** Adverse Drug Reactions related to potentially inappropriate medication, according to ICD-10 (n=17)

ICD-10	Frequency n (%)	ADR to PIM
Symptoms, signs and abnormal clinical and laboratory findings, not classified elsewhere	7 (41.2)	dizziness (2), fatigue (2), headache (1), fever (1), tremor (1)
Digestive system	3 (17.6)	stomach pain (1), diarrhea (1), abdominal pain (1)
Respiratory system	2 (11.8)	breathlessness (1), cough (1)
Skin and subcutaneous tissue	2 (11.8)	erythema (2)
External causes	2 (11.8)	digoxin toxicity (2) – nausea, vomiting and visual changes
Circulatory system	1 (5.8)	arrhythmia (1)

## DISCUSSION

The present study observed that approximately one out of five (59/308) older people reported taking PIM before hospital admission. This prevalence is apparently underestimate, since data in literature show that 24.5% to 66.0% of older people use PIM [8,11-16]. The low percentage found can be explained by underreporting of data, since it was not possible to interview all older patients admitted to internal medicine ward. Furthermore, it is probable that several of them did not remember to report all drugs taken and this information is not available in medical records, because these documents generally have not got the register of drugs used by community-dwelling patients. Data suggest a need for health institutions to promote training and habilitation of health professionals, qualifying them to identify medication errors and avoid the misuse of drugs, as well as to regulate the correct fill of medical records, in order to contemplate the pharmacological anamnesis at the time of hospital admission. These measures can contribute for early detection of drug related problems (DRP) and negative outcomes associated with medication (NOM), besides to target the rational pharmacotherapeutic management during all length of stay of patient in the hospital.

Studies conducted in hospitals have estimated that 10.0% to 49% [8,12,15] of the older people that take PIM are hospitalized because of ADR. However, there is controversy regarding whether the use of PIM is a risk factor for hospital admission [10,12,13,16]. In this study, one out of four (15/59) patients who reported taking PIM had been admitted to hospital for ADR. However, the use of these drugs was not detected as a risk factor for the occurrence of ADR. Probably, severe ADRs that lead to hospitalization may be caused by idiosyncratic response or predisposition of older people to develop adverse reactions, not necessarily related to the type of drug used.

Albert et al. (2010) [22], after adjusting for the variables age, gender, presence of serious diseases and number of drugs prescribed, found that older people who had used PIM were 1.8 to 1.9 times more likely to be hospitalized. Our finding shows that gender and age was not a risk factor for the occurrence of ADR to PIM, and corroborates the results of studies performed by Gallagher et al. (2008) [8] and Akazawa et al. (2010) [11], since age categories had no association with PIM use. The authors of Japanese research [11] explain their findings based on data collection that was performed in a health system database, in which the proportion of elderly patients aged  $\geq 65$  years was very low. Furthermore, these elderly patients tended to be younger and healthier than the general elderly population. In Brazil, owing to life expectancy to be 73.2 years [23] there are few elderly aged  $\geq 75$  years, who contemplated groups III and IV. This fact may explain why there is no evidence that use of PIM increase in advance aged and can raise the susceptibility of elderly to develop ADR.

Ethanol consumption and smoking habit were variables studied, since they may be involved in pharmacokinetic or pharmacodynamic interactions and can increase the likelihood of development of adverse drug events (ADE) in drug takers. Moreover, there is a problem of non-adherence to pharmacotherapy in users of alcohol [24] and tobacco [25] with chronic diseases (e.g. AIDS), that could increase the prevalence of DRP; NOM and failure of the treatment. These factors can be related to hospitalization. Therefore, health professionals should have continuing education in order to detect possible risk factors for hospital admissions and properly orient the patient to minimize the hazardous caused by the association of medication, alcohol and tobacco, whether the patient refuses to give up the addiction. However, there was no association between ethanol consumption and smoking habits and reasons for hospitalization, since few older people reported the use of these

substances. This may reflect the incentives that the World Health Organization has offered to reduce and prevent smoking<sup>[26]</sup> or due to patients not report the consumption of tobacco and / or ethanol, knowing that it is inappropriate socially practice and injurious to health.

Polypharmacy has been reported as one of the factors that most contribute to hospitalizations due to ADR. Chang et al. (2005)<sup>[27]</sup> found that in patients who had PIM prescribed, the number of prescribed drugs was not significantly associated with ADRs [RR = 0.8, 95% CI (0.6-1.1)]. However, we found that older patients with ADR to PIM had taken more drugs, prior to hospitalization, than patients hospitalized for other reasons ( $p = 0.02$ ). This finding was expected, since elderly are most affected by chronic diseases that need pharmacological treatment to control them. Therefore, they usually take more drugs, which could raise the odds of being prescribed PIM<sup>[17]</sup> and this fact may contribute for the development of NOM, such as ADR.

Page et al. (2006)<sup>[28]</sup> found that inappropriate drugs used by seniors adults were not statistically related to the period of hospitalization. However, our data show that the length of stay of older people who had ADR to PIM was shorter than that of patients without identified ADR ( $p = 0.04$ ). This data remit an important issue that is common among older people: the under-treatment of their health conditions. In Brazil, there is a lack of knowledge in pharmacovigilance of health professionals, hindering them to predict and prevent ADR<sup>[15]</sup>, mainly when the clinical manifestations are unspecific, as occurred in the present study. These factors may be explained the early discharge of patients with ADR to PIM.

Regarding the identified PIM, 55.0% of them were related to ADR, of which 73% (8 / 11) are frequently prescribed for older people, according to the literature: digoxin<sup>[8-10,14,16,29]</sup>, amitriptyline<sup>[9,10,13,14,16,29]</sup>, amiodarone<sup>[8-10,14,16,29]</sup>, diazepam<sup>[10-14]</sup>, methyl dopa<sup>[9,10,12,17,29]</sup>, cimetidine<sup>[9-11,16,29]</sup>, fluoxetine<sup>[9,10,14,16,29]</sup> and short-acting nifedipine<sup>[8-10,14,16]</sup>. Data suggest that prescribers do not know the drugs considered PIM for older people, since there are safer alternatives for most inadequate medications identified in the present study, such as selective serotonin reuptake inhibitors or serotonin-specific reuptake inhibitor (e.g. sertraline) and short-acting benzodiazepines (e.g. lorazepam). However, several safer equivalent therapeutics can not be prescribed in public Brazilian health institutions, because they are not available for use, since the selection of

drugs is based on national list of essential medicines. Therefore, it is necessary to evaluate the possibility of inclusion of safer therapeutic alternatives for elderly in national list of essential medicines (e.g. sertraline and short-acting benzodiazepines) and in WHO Model List of Essential Medicines (which has not contain, e.g., sertraline), as well as to promote wide dissemination for physicians and other prescribers of criteria or tools that list PIM, in order to improve the quality of prescription for elderly and contribute for correct use of drugs.

Moreover, it is important to note that in the present study 7% (1 / 15) of the older people had taken PIM that belonged to criteria II (interaction of nonselective  $\beta$ -blockers with chronic obstructive pulmonary disease). This finding corroborates the study performed by Christillies et al. (2009)<sup>[13]</sup>, since they found the same disease-drug interaction. Considering these findings, there is evidence that exist failures in communication between health professionals and their patients. Therefore, it is necessary to improve the interaction between the multidisciplinary teams at all levels of health care, to provide a holistic view of problems and needs of the patient. Such measures could improve clinical evaluation and allow prescription of rational pharmacotherapy.

The commonest manifestations of the ADR were: dizziness, fatigue, digoxin toxicity (evidenced by the classic symptoms of intoxication - nausea, vomiting and blurred vision, as well as by laboratory tests - toxic plasmatic concentration of the drug) and erythema, which totaled 47% of ADRs identified. Gallagher et al. (2008)<sup>[8]</sup> and Laroche et al. (2007)<sup>[12]</sup> also observed that digoxin toxicity was one of the most frequent undesirable effects of PIM. Therefore, pharmacotherapeutic follow-up of the use of digitalis and the management of serum levels of digoxin is relevant to prevent the toxic effects of this therapy, since it is a drug with narrow therapeutic range.

### **Study limitations**

The different prevalences of ADR to PIM related to hospital admissions observed in the present study and other researches can be explained due to study design, location and methods used to analyze ADR. Furthermore, the prevalence estimated may be underestimated, since several patients could not be interviewed and due to Beers criteria, since this method does not cover all drugs available in Brazil and include several drugs that have not been approved for use in our country. Therefore, it is hard to do any inferences

in causation (use of PIM and risk of hospitalization for ADR). Furthermore, our study has selection bias, since data were collected in a ward of a hospital of high complexity. Thus, other limitation is the generalization from findings. Moreover, due to the majority of data collected came from the elderly volunteer patients who self-reported the drugs taken prior to hospitalization, there is also bias on data analysis. Older people generally had cognitive impairment and deficit on memory, being unlikely that all interviewed patients remembered all drugs administered before hospitalization, even reporting that they were able to say all medications used. This fact can contribute for underestimation of the prevalence of hospitalization due to ADR to PIM. Besides, some of ADR identified can be developed by off-label use. Meanwhile, these cases could not be evaluated, since our form not cover all necessary issues to analyze off-label use, because (1) it was not an objective of the study, (2) the study subjects were patients hospitalized, who comprised elderly people who did not know if the indication of their medication was right, (3) we did not have the possibility to interview the physicians who prescribed the drugs regarding off-label use, because they were not linked in the hospital studied.

## CONCLUSION

Although the use of PIM was not detected as a risk factor for occurrence of ADR, high prevalence of hospitalizations related to the use of these drugs was observed. Owing to life expectancy in Brazil to be 73.2 years old and characteristics of high complexity of the hospital, featuring care of patients with severe diseases, only polypharmacy was detected as a risk factor for the occurrence of ADR to PIM. The commonest clinical manifestations of adverse reactions were the signs and abnormal clinical and laboratory findings not classified elsewhere, according to ICD-10, which were caused mainly by drugs acting on the nervous system (45.4%) and cardiovascular tract (36.4%). Therefore, continuing education should be providing for all health professionals in order to qualify them to predict medication errors and to prevent hazardous for elderly people.

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