



## Potentially Inappropriate Medication Use Among Brazilian Elderly: A Population-Based Pharmacoepidemiological Study

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**SUMMARY.** Potentially inappropriate medications (PIMs) for the elderly can be associated with greater risks than benefits and its use has been reported internationally. A cross-sectional study was performed based on data from a representative sample of the elderly population (60 years or older) living in the Metropolitan Region of Belo Horizonte (n=1,158). The dependent variable was PIM use (2012 Beers Criteria). The independent variables included sociodemographic characteristics, health status and use of health care services and medications. Analyses were performed using Poisson regression model at a level of significance of 5%. The prevalence of PIM use was 43.3% and a total of 694 PIMs were identified. After multivariate analysis, female gender, number of chronic conditions and number of medications were positively and independently associated with PIM use. The study revealed a high prevalence of PIM use, indicating the need for selection of safer therapeutic alternatives in this patient group.

**RESUMEN.** Los medicamentos potencialmente inapropiados (PIM) para personas mayores pueden estar asociados con mayores riesgos que beneficios y su uso se ha reportado internacionalmente. Se llevó a cabo un estudio transversal sobre la base de datos de una muestra representativa de la población de edad avanzada (60 años o más) que viven en la Región Metropolitana de Belo Horizonte (n = 1.158). La variable dependiente fue el uso de PIM (2012 Beers Criteria). Las variables independientes incluyeron características sociodemográficas, estado de salud y el uso de los servicios de salud y medicamentos. Los análisis se realizaron utilizando el modelo de regresión de Poisson a un nivel de significación de 5%. La prevalencia del consumo de PIM fue de 43,3% y se identificaron un total de 694 PIM. Tras el análisis multivariante, el sexo femenino, el número de enfermedades crónicas y el número de medicamentos fueron positiva e independientemente asociados con el uso de PIM. El estudio reveló una alta prevalencia del consumo de PIM, lo que indica la necesidad de una selección de alternativas terapéuticas más seguras en este grupo de pacientes.

### INTRODUCTION

The increased demographic representativeness of the elderly is a global phenomenon attributed to a fall in death, birth and fertility rates together with an increase in life expectancy at birth<sup>1,2</sup>. However, the aging of the Brazilian population stands out in the context of epidemiological discussions because this process has been both rapid and marked: between 1960 and 2010, the number of Brazilian elderly increased almost 7 fold (from 3 million to 20.5 million)<sup>3,4</sup>.

Demographic transformations in the Brazilian

population have been accompanied by epidemiological transformations with substantial changes in the morbimortality pattern<sup>5</sup>. In 1930, infectious and parasitic diseases were the cause of around 45% of all recorded deaths nationwide. Currently, estimates suggest that chronic non-communicable diseases (CNCDs) are now the leading cause of death (72%), with the elderly population particularly affected<sup>5-7</sup>.

The high, multiple prevalence of CNCDs (and their consequent clinical sequelae) in elderly leads to a high degree of dependence,

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calling for permanent medical treatment and multi-disciplinary teams, hospital care, continuous interventions and use of a number of medications<sup>4,8,9</sup>. In this regard, the safety of medications used represents a critical aspect in the health care of the elderly population, and appropriate prescribing is one of the most important indicators for assessing this safety<sup>10,11</sup>.

The choice of medication for the treatment of the elderly should be made with caution, since the use of some drugs in this age group can be associated with greater risks than benefits<sup>11</sup>. Identifying inappropriate medications and avoiding their prescription is a practice that promotes the safe and rational use of medications. Beers Criteria is an important tool for this practice, since it lists potentially inappropriate medications (PIMs)<sup>10</sup>.

PIM use has been associated with increased risk of the occurrence of many drug-related adverse events<sup>12,13</sup> such as falls, fractures, gastrointestinal bleeding, constipation, exacerbation of congestive heart failure, depression and renal failure<sup>10,11</sup>. In addition, prescribing PIMs was also shown to be associated with higher mortality<sup>14</sup> and hospitalization in older adults<sup>12-14</sup>.

The use of these medications among elderly has been reported internationally in long-term care institutions<sup>15,16</sup>, hospitals<sup>17-20</sup> and in the community<sup>21-23</sup>. However, there is a dearth of Brazilian population-based, pharmacoepidemiological studies investigating the use of PIMs with the latest updated version of Beers Criteria<sup>10</sup>.

In light of these issues, the objective of the present study was to estimate the prevalence of PIM use among elderly from the Metropolitan Region of Belo Horizonte (MRBH), Minas Gerais, and to identify the factors associated with this practice.

## METHODS

### Study area and population

The present cross-sectional investigation was carried out in the Metropolitan Region of Belo Horizonte (MRBH), the third most populous metropolitan region in Brazil at the time of the study (4.4 million, encompassing 20 cities). The study population comprised a representative sample of the elderly population (60 years or over – as defined by the World Health Organization in the case of developing countries) residing in the community of the cities within the MRBH.

The sampling design was clustering sampling, yielding a complex sample, whose prima-

ry sampling unit was census sector and secondary sampling unit was household. The sample size (7,500 households) was designed in order to produce estimates for the adult population residing in 24 cities that compose the MRBH and to allow a more specific and profound study regarding the elderly population, age group of interest for the present study which constitutes 8% of the MRBH total population. The experience of similar epidemiological researches developed in other Brazilian metropolitan regions, which held sample losses up to 20%, were also taken into consideration. From the 24,000 individuals residing in the selected households, 1,774 were elderly and 1,635 agreed to participate in the study (92.2%). The sex and age distribution in the sample was similar to that detected in the MRBH population<sup>24</sup>.

### Study variables and data collection

The dependent variables of the study were PIM use, independent of drug-disease or drug-syndrome interactions, according to Beers Criteria<sup>10</sup>. PIM were also grouped into intermediate groups corresponding to therapeutic classes (e.g. first generation anti-histamines, antiparkinson agents, antispasmodics, alpha1-blockers, central alpha agonists, antiarrhythmic drugs, tertiary tricyclic antidepressants, first and second generation antipsychotics, barbiturates, benzodiazepines) or groups with a single representative (e.g. dipyridamole, ticlopidine, nitrofurantoin, digoxin, immediate release nifedipine, spironolactone, chloral hydrate, meprobamate). Data used for measuring PIMs was derived from self-reported use of medications in the last 15 days by the interviewee, with concomitant checking of the prescriptions and medication packages by the interviewer. The medications reported by the participants were identified and their active ingredients and dosages determined.

The independent variables were grouped into three sub-groups: sociodemographic characteristics, health status and health care service utilization. The sociodemographic variables included gender, age (60-69 years; 70-79 years;  $\geq$  80 years), total years of schooling completed (< 4 years; 4-7 years;  $\geq$  8 years) and living alone (yes *versus* no). Health status was based on self-rated health status (very good/good; moderate; bad/very bad) and the number of selected chronic conditions (< 2; 2-3;  $\geq$  4). Chronic conditions were surveyed based on self-reported history of medical diagnosis for these diseases, covering arthritis/rheumatism, cancer, systemic

arterial hypertension, asthma/bronchitis, diabetes mellitus, coronary heart disease, stroke, chronic kidney disease, spinal disease/back pain and depression. Health care service utilization encompassed the number of medical appointments in the last 12 months (< 3; 3-5; and  $\geq$  6), history of hospital admission in the last 12 months (yes *versus* no), coverage by a private health care plan (yes *versus* no) and number of medications used (1; 2-4 and  $\geq$  5).

Data was collected manually by duly trained interviewers at participants' homes between June and July 2003. Further details can be found in another publication <sup>24</sup>.

### Data analysis

The prevalence of PIM use was estimated based on the proportion of interviewees reporting the use of at least one PIM. Comparison of the PIM user versus the non-user groups was performed using Pearson's Chi-square test with application of the Rao & Scott correction factor. Univariate and multivariate analyses were based on prevalence ratios and respective 95% confidence intervals, estimated by the Poisson regression model, with a robust variance. All independent variables were included in the multivariate model, independently of results on the respective univariate analyses. A level of significance of  $p < 0.05$  was the criteria adopted for identifying the characteristics independently associated with PIM use in the multivariate model. All statistical analyses were performed using version 13 of the Stata<sup>®</sup> statistical package, deploying the resource for analyzing complex samples (*svy* command).

### Ethical aspects

The present investigation was approved by the ethics committee of the René Rachou Research Center/Oswaldo Cruz Foundation (report 011/2001), where secrecy of the identity of participants and confidentiality of the information were guaranteed. All participants signed the Free and Informed Consent Form prior to application of the questionnaire.

### RESULTS

Of the total elderly subjects initially interviewed ( $n = 1,635$ ), 1,158 were subsequently included in the study, having reported use of at least one medication. Participants had a mean age of 70.4 years (minimum = 60; maximum 97) and were predominantly female (65.3%); subjects had a low education level (43.0% had less

than four years of formal education) and a small proportion lived alone (12.7%). Regarding health status, 15.9% of the elderly rated their health as "bad" or "very bad" and 87.1% reported harboring at least one chronic condition. For health care service utilization, 52.1% of subjects had no private health care insurance plan, 35.0% had attended six or more medical appointments, and 17.3% had a history of hospital admission in the last 12 months; in addition, the majority (75.4%) of the elderly reported use of two medications or more.

The prevalence of PIM use was 43.3% (CI<sup>95%</sup> 40.1-46.5); the prevalence in the reference population (including non-users of medication) was 30.4% (CI<sup>95%</sup> 27.9-32.9). The number of PIMs used ranged from one to seven, where most medication users (29.9%) reported use of a single PIM.

Overall, a total of 694 PIMs were used, most notably immediate release nifedipine ( $n = 82$  or 11.8%), glibenclamide ( $n = 70$  or 10.1%), digoxin at a daily dose exceeding 0.125 mg ( $n = 63$  or 9.1%) and diclofenac ( $n = 55$  or 7.9%). According to the intermediate groups (proposed in Beers criteria), besides immediate release nifedipine (qualified previously), the main PIMs were benzodiazepines ( $n = 89$  or 12.8%), sulfonyleureas ( $n = 78$  or 11.2%) and non-steroidal anti-inflammatory drugs (NSAIDs;  $n = 73$  or 10.5%). Table 1 lists 10 groups of the most commonly used PIMs, accounting for approximately 80% of all PIMs reported.

Table 2 depicts the results of the univariate analysis of factors associated with PIM use. With the exception of age, living alone and having a health care insurance plan, all other factors were associated with the event, at a 5% level of significance.

The final results of the multivariate analysis are given in Table 3. PIM use showed significant positive association with female gender (PR 1.18; CI<sup>95%</sup> 1.00-1.39), with use of two medications or more (PR 2.14; CI<sup>95%</sup> 1.55-2.96 for "2-4 medications"; PR 3.20; CI<sup>95%</sup> 2.29-4.46 for " $\geq$  5 medications") and with number of chronic conditions (PR 1.28; CI<sup>95%</sup> 1.04-1.56 for  $\geq$ 4 chronic conditions).

### DISCUSSION

To date, few studies have employed Beers 2012 criteria to investigate the prevalence of PIM use among community-dwelling elderly. To our knowledge, this is the first study involving a population-based sample conducted in Brazil.

Medication	Absolute frequency (n)	Relative frequency (%)
Benzodiazepines	89	12.8
Immediate release nifedipine	82	11.8
Sulfonylureas	78	11.2
Non-COX selective nonsteroidal antiinflammatory drugs	73	10.5
Digoxin > 0.125 mg/day	63	9.1
Alpha agonists	45	6.5
Tertiary tricyclic antidepressants	42	6.1
Estrogens	42	6.1
Antiarrhythmic drugs	39	5.6
Spironolactone > 25 mg/day	29	4.2
Others	112	16.1

**Table 1.** Frequency of potentially inappropriate medication use according to Beers criteria. Metropolitan Region of Belo Horizonte, Brazil, 2003.

The high prevalence of this event detected in the present study (43.3%) mirrors results observed among Spanish older adults (44%)<sup>21</sup>, and among older people aged 75 years or over from New Zealand (42,7%)<sup>23</sup> but was greater than the rates detected among Irish older adults aged 70 years and over (28%)<sup>22</sup>.

In the present study, the most frequently used PIMs belonged to the therapeutic classes of benzodiazepines, sulfonylureas and NSAIDs, whereas immediate release nifedipine was the main active principle ingredient. The presence of benzodiazepines and NSAIDs (more specifically, diclofenac) among the most used PIMs was also observed in elderly from high-income countries<sup>21-23</sup>.

The use of benzodiazepines among elderly, common in a range of different settings, is marked and had been previously reported by other Brazilian studies<sup>25-27</sup>. Benzodiazepines are frequently used to manage mild to moderate sleep disorders and anxiety, even though it has been issued that those are not drugs of choice for such health conditions, especially among aged patients<sup>28</sup>. The use of this group of PIMs in elderly calls for caution and continuous follow-up of the pharmacotherapy, because they are known to predispose this population to adverse events such as sedation, *delirium*, cognitive deficits, falls and fractures<sup>10,29-32</sup>. Benzodiazepines should be administered only after non-pharmacological interventions (*e.g.* sleep hygiene and relaxation) and other safer first line pharmacological treatments such as serotonin re-uptake inhibitors (SSRIs) have proven ineffec-

tive<sup>28,33</sup>. Even when the patient presents generalized anxiety disorder, benzodiazepines should not be used as first therapeutic choice. Their use should be limited to short term relief (2 to 4 weeks only) in crisis situations such as anxiety or insomnia that are severe and disabling<sup>28</sup>.

The use of NSAIDs is common among elderly to manage pain due to osteoarthritis, which prevalence in the population studied was 19.5% (results not shown). However, even though pain has strong and negative impacts on quality and quantity of life, safety is a major concern when it comes to pharmacological management in chronic conditions such as osteoarthritis that require long-term treatment<sup>34</sup>. This class of medication is directly associated with the development of gastrointestinal bleeding/peptic ulcers, and studies suggest that the risk of manifesting gastrointestinal problems as a result of its use increases 2 to 2.5-fold among individuals aged 60 or older<sup>10,35,36</sup>. Moreover, studies indicate that NSAID use (particularly diclofenac, the most used anti-inflammatory in the population investigated) is associated with increased cardiovascular as well as renal risk<sup>35,37,38</sup>. In elderly, the use of these agents, especially non-selective NSAIDs, should be restricted and involve the lowest therapeutic doses possible, and be accompanied by peptic ulcer prophylaxis using proton pump inhibitors<sup>10,36</sup>. Preference should be given to topical NSAIDs which, while exhibiting similar therapeutic efficacy to oral NSAIDs for controlling osteoarthritis-related pain, have fewer systemic adverse effects<sup>35,39</sup>. In addition, choice of NSAIDs for pain manage-

Variables		PIM Use (%)		PR (95%CI) *	p-value**
		Yes	No		
Gender	Male	64.0	36.0	1.00	-
	Female	52.8	47.2	1.31 (1.11-1.56)	0.002
Age (years)	60-69	55.6	44.4	1.00	-
	70-79	56.6	43.4	0.97 (0.83-1.15)	0.782
	≥80	60.9	39.1	0.88 (0.69-1.12)	0.302
Schooling (total years completed)	<4	52.4	47.6	1.00	-
	4-7	54.9	45.1	0.95 (0.81-1.11)	0.508
	≥8	66.5	33.5	0.70 (0.57-0.88)	0.002
Living alone	No	56.7	43.3	1.00	-
	Yes	56.6	43.4	1.00 (0.80-1.25)	0.982
Self-rated health status	Very good/Good	69.2	30.8	1.00	-
	Moderate	49.0	51.0	1.66 (1.37-1.99)	<0.001
	Bad/Very bad	47.2	52.8	1.72 (1.37-2.14)	<0.001
Number of chronic conditions	<2	68.4	31.6	1.00	-
	2-3	51.1	48.9	1.55 (1.29-1.86)	<0.001
	≥4	39.2	60.8	1.92 (1.58-2.34)	<0.001
Number of medical appointments	<3	67.6	32.4	1.00	-
	3-5	52.5	47.5	1.47 (1.19-1.81)	<0.001
	≥6	51.0	49.0	1.51 (1.24-1.86)	0.001
Hospitalization	No	59.4	40.6	1.00	-
	Yes	43.8	56.2	1.38 (1.18-1.62)	<0.001
Use of private health care plan	No	55.9	44.1	1.00	-
	Yes	57.5	42.5	0.96 (0.83-1.12)	0.632
Number of medications used	1	82.1	17.9	1.00	-
	2-4	55.3	44.7	2.50 (1.81-3.44)	<0.001
	≥5	29.0	71.0	3.97 (2.89-5.46)	<0.001

**Table 2.** Results from univariate analysis of associated factors with potentially inappropriate medication (PIM) use. Metropolitan Region of Belo Horizonte, Brazil, 2003. \*Prevalence ratio (95%CI) estimated by the Poisson regression method. \*\*Poisson Regression; significant when  $< 0.05$ .

ment in osteoarthritis should be careful and take into considerations the different profiles of heart and gastrointestinal safety <sup>34</sup>.

The number of medications is the characteristic consistently associated with PIM use in other countries <sup>21,23</sup>. In the present study, the prevalence of PIM use was significantly higher among participants who were in use of two medications or more, where greater polypharmacy (5 medications or more) was the characteristic most strongly associated with the event. This may indicate that the number of medications serves as a proxy for PIM use, rendering this characteristic useful for screening elderly at potential risk of using this group of medications, and consequently having greater exposure to

the adverse events associated with their use. This potential risk marker can be used to identify those elderly patients that constitute preferential targets for the development of strategies to improve their pharmacotherapy.

The positive association between female gender and PIM use detected in this study was not observed in international studies <sup>21,23</sup>. Women's higher propensity to report health problems and utilize health care services is the explanation usually given for the greater use of medications (in general) by women compared to men <sup>40,41</sup>. However, it is important to bear in mind that women tend to use a greater number of PIMs than men even when receiving similar health care <sup>42</sup>. Furthermore, in the present study,

Variables		PR (95%CI) *	p-value**
Gender	Male	1.00	-
	Female	1.18 (1.00-1.39)	0.042
Age (years)	60-69	1.00	-
	70-79	0.92 (0.80-1.07)	0.305
	≥80	0.79 (0.62-1.00)	0.053
Schooling (total years completed)	<4	1.00	-
	4-7	0.97 (0.82-1.14)	0.707
	≥8	0.85 (0.67-1.07)	0.154
Living alone	No	1.00	-
	Yes	0.89 (0.72-1.10)	0.292
Self-rated health status	Very good/good	1.00	-
	Moderate	1.19 (0.98-1.44)	0.083
	Bad/Very bad	1.16 (0.91-1.47)	0.222
Number of chronic conditions	<2	1.00	-
	2-3	1.15 (0.96-1.39)	0.132
	≥4	1.28 (1.04-1.56)	0.019
Number of medical appointments	<3	1.00	-
	3-5	1.10 (0.90-1.34)	0.361
	≥6	0.99 (0.81-1.20)	0.916
Hospitalization	No	1.00	-
	Yes	1.07 (0.92-1.24)	0.392
Use of private health care plan	No	1.00	-
	Yes	1.01 (0.86-1.19)	0.883
Number of medications used	1	1.00	-
	2-4	2.14 (1.55-2.96)	<0.001
	≥5	3.20 (2.29-4.46)	<0.001

**Table 3.** Results of multivariate analysis of associated factors with potentially inappropriate medication (PIM) use. Metropolitan Region of Belo Horizonte, Brazil, 2003.\*Prevalence ratio (95%CI) estimated by the Poisson regression method, \*\*Poisson Regression; significant when < 0.05.

the female sex was independently associated with PIM use, where this association remained independent even after exclusion of the estrogens therapeutic class from the analysis (results not shown in table), which were identified as a PIM used specifically by women in this age group.

Number of chronic conditions, a variable not assessed in international studies, was also associated with PIM use. This association is likely due to the fact that the majority of PIMs used constituted classic therapeutic options for managing health conditions prevalent in this population, such as arthritis/rheumatism and back pain (NSAIDs), and diabetes mellitus (sulfonylureas).

The present study has some limitations. The first is that Beers criteria could not be applied in full, since the identification of PIMs due to drug-disease or drug-syndrome interactions was not

possible because of the non-inclusion of various health conditions in the questionnaire employed. Also, given the posology of the medications used was not recorded during data collection (only the dosage and pharmaceutical form), in cases of medications whose inappropriate status was based on daily dose (e.g.: digoxin at doses exceeding 0.125 mg/day; spironolactone at doses exceeding 25 mg/day), PIM use may have been under or over-estimated, since half a tablet (overestimation) or two or more tablets (underestimation) may have been prescribed. Even after excluding digoxin and spironolactone, however, the prevalence of PIM use among users of medications was still high, at 39.2% (95%CI 36.0-42.3).

Another limitation is that this study retrospectively applied the 2012 version of the Beers criteria. However, it was not the objective of this

study to draw conclusions about the quality of the prescription at the time of collection (2003) but to address, in a significantly sized Brazilian elderly sample, the association between PIM use and different sociodemographic characteristics, health status and health care service utilization that are still relevant. The retrospective analysis is pertinent, given the fact that the most used PIM identified in the present study, to date, are present in the Brazilian Essential Medicines List<sup>43</sup>. They are also identified as the most used PIM in other recent Brazilian and international studies<sup>21-23,25-27</sup>.

Nevertheless, the study results reported are unique in that they are the first characterizing PIM use in a large population-based sample of the 3<sup>rd</sup> largest metropolitan region in Brazil with the updated version of Beers criteria.

## CONCLUSIONS

The results for prevalence and associated factors found in the present study corroborate the finding of previous studies conducted in other elderly populations, more specifically, those living in high-income countries. The high prevalence of PIMs use found highlights the need for similar investigations to be run on a routine basis in a bid to reduce the risks associated with the pharmacological therapeutics prescribed to elderly. Given that the elderly segment is a major user of medications, the selection of safer alternative therapeutics, rigorous follow-up and identification of negative outcomes associated with PIMs use (when prescribing these drugs cannot be avoided) is important in routine clinical practice.

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