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Article

# Potentially inappropriate medication use in a comprehensive therapy management service: clinical outcomes and interventions

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This study aimed to describe potentially inappropriate medication (PIM) use according to the Beers criteria among older adults followed in a comprehensive medication management (CMM) service, the pharmacists´ interventions, and the clinical outcomes of PIM use. All older adults in a CMM service delivered in the Brazilian public primary care system were included in the study (n = 389). Two methodological approaches were developed: (I) cross-sectional - prevalence of PIM use and associated factors were identified (univariate analysis – Pearson's chi-square; multivariate – logistic regression); (II) documental analysis of the negative clinical outcomes potentially associated with PIM use and pharmacists' interventions. The prevalence of PIM use was 48.3%, and it was independently and positively associated with the use of ≥ 5 drugs. For 21.3% of PIMs, a potential negative clinical outcome was identified. The most common negative clinical outcome was hypotension (35.1% of the negative outcomes), fractures or diagnosis of osteoporosis (21.1%), and hypoglycemia (14.0%). For most of them (78.9%), an intervention was performed to mitigate harm or discontinue use. A high prevalence of PIM was detected and was associated with polypharmacy. A significant proportion of PIM showed potential negative clinical outcomes that were identified by clinical pharmacists, and the majority of pharmacists' interventions aimed at its mitigation or deprescription. Overall, our findings reinforce the potential of CMM services for reducing PIM use and the occurrence of negative outcomes.

**Keywords:** Brazil. Aged. Medication therapy management. Potentially inappropriate medication list. Pharmaceutical care.

## INTRODUCTION

The Brazilian population has been aging rapidly. The national age pyramid underwent changes in the late 1960s, but now, it considerably resembles those in developed countries (Vasconcelos, Gomes, 2012). In middle income countries such as Brazil, elderly individuals are defined as those who are 60 years or older and this aged Brazilian population increases by 700 thousand individuals per year (IBGE, 2013). In 2012, the number of individuals in this age group was 23.5 million, representing 12.6% of the population (IBGE, 2013), and in 2020, this number is expected to reach the 30 million mark, which will make Brazil the

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sixth country in the world with the largest number of aged people (Veras, Xavier, 2009).

Even though the aging process has to be celebrated as a positive sign of healthcare improvement, it changes the mortality, morbidity, and medication use patterns in society and brings new challenges to the multidisciplinary team (Schmidt *et al*., 2011). It is estimated that more than 85% of the elderly have at least one chronic disease and about 10% present comorbidities (Gonçalves *et al*., 2006) that often demand the use of multiple medications (Hajjar, Cafiero, Hanlon, 2007; Gurwitz, 2004). However, some of these medications present potential risks that outweigh the therapeutic benefits for the aging population (AGS, 2019). These are called Potentially Inappropriate Medications (PIM) for older adults and their use should be avoided in the elderly, especially when there are safer therapeutic alternatives that can be used for the same clinical condition (AGS, 2019; O'Mahony, 2010).

The Beers Criteria (AGS, 2019) is an explicit criterion that lists the PIM that have been used in numerous countries in different scenarios and have been shown to be associated with the occurrence of adverse events, hospitalization, and even mortality (Nascimento *et al*., 2017; Price *et al*., 2014). However, this group of medication is still frequently prescribed at the international level (Grina, Briedis, 2017; Novaes *et al*., 2017; Skaar, O'Connor, 2017) and few studies have demonstrated comprehensive initiatives to reduce or qualify its use (Caffiero *et al*., 2017; Viswanathan *et al*., 2015). Thus, it is important to describe the factors associated with PIM use, and, specially, to evaluate its clinical impact, and strategies, including pharmaceutical services, that can reduce its overall use.

Therefore, this study aimed to investigate PIM use among older adults followed-up in a Brazilian comprehensive medication management (CMM) service, to describe the negative clinical outcomes potentially associated with PIM use, and the interventions performed by pharmacists during the provision of this clinical service in face of PIM prescription and use.

## MATERIAL AND METHODS

### Setting and population

The CMM service described in this paper is provided by the public primary health care system of a mid-sized city of the Minas Gerais State, Brazil. Primary care is the base of the Brazilian healthcare system and is offered in every single state, with each state being divided according to health districts. The service is provided in all of the city's districts and began to be offered in April 2015; every patient aged 60 years old or more (cut-off point for aged adults in Brazil and other low- and middle-income countries) who attended this service up until February 2016 was included in the present study (n = 389). The service has an open demand, therefore, no specific inclusion criteria were established for patient referral.

### The CMM service

The CMM service studied is provided by five clinical pharmacists hired exclusively for such activity. The patient care process adopted fully followed the theoretical framework of the Pharmaceutical Care Practice. Therefore, the adopted patient care process was the Pharmacotherapy Workup method (Cipolle, Strand, Morley, 2004). In this process, during each encounter, a clinical pharmacist performed an assessment of drug therapy (prescribed and non-prescribed) for all the patient´s health problems to identify and resolve drug therapy problems (DTP) and promote optimal patient outcomes. To meet those goals, the pharmacists evaluate the effectiveness and safety pharmacotherapeutic parameters and perform interventions with both the prescriber (easily accessible in the study scenario) and the patients whenever needed. The initial assessment usually takes 1–1.5 h and the following evaluations take 0.5–1 h.

### Study design and data collection

The present study was divided in two methodological approaches in order to achieve the proposed objectives: (Step I) – a cross-sectional design; and (Step II) – a documental analysis. All the necessary data were

extracted retrospectively from the CMM documentation system that stored all the patients' records and were recorded in an anonymous database in Stata® statistical package (Version 12).

*Step I - Cross-sectional design*

A cross sectional design was used to describe the prevalence of PIM use in the first two CMM consultations and the associated factors. To this end, the following data were collected: gender, age, health problems, and medications used.

The data related to the medication used (prescribed and non-prescribed) were those identified in the first and second CMM consultation by the pharmacist through simultaneous verification of the prescription orders and medication packages. The medications were identified and broken down into their active ingredients, dosages, and pharmaceutical forms. These were later classified as PIM according to the 2015 Beers criteria (AGS, 2015). The PIMs were also grouped in intermediate categories corresponding to the therapeutic classes or categories with a single representative, as proposed by the criteria. Despite the existence of multiple explicit method to identify PIM (Motter *et al*., 2018; Varallo *et al.,* 2014), the Beers criteria was the chosen in the present study given its that it is easily applicable in large data sets as the one used in the present study. In addition, the Beers criteria is the most internationally applied PIM criteria and has a robust method for its development, that involves a systematic review of literature and extensive validation and grading by selected experts and also by external organizations and public (AGS, 2015).

The prevalence of PIM use was estimated by the proportion of patients presenting documentation of the use of at least one PIM in the first and/or second CMM consultation. It was also defined as the dependent variable for the cross-sectional design, and its association with the following independent variables was investigated: gender, age, number of health problems, and number of medications used.

All the quantitative variables were dichotomized according to their median. The descriptive analysis was performed by determining the absolute and relative frequencies of the categorized variables, as well as the mean and amplitude of variables. Univariate analyses were performed using the Pearson chi-square test. With all the independent variables considered relevant, a parsimonious model was constructed with their inclusion in the multivariate logistic regression regardless of the univariate analysis result. A likelihood ratio test was used to compare the multivariate models and the Hosmer-Lemeshow test was used to evaluate goodness of fit. The univariate and multivariate analyses were based on the odds ratio (OR) and their respective 95% confidence intervals (95% CI) were estimated by logistic regression. A 5% level of significance was the criteria adopted for identifying the characteristics independently associated with the dependent variable. All statistical analyses were performed using version 12 of the Stata® statistical package.

*Step II – Documental Analysis*

The occurrence of negative clinical outcomes potentially associated with PIM use and the pharmacists' interventions performed were evaluated by analyzing the pharmacotherapy workup process documented in the CMM documentation system in all consultations.

The "negative clinical outcomes potentially associated with PIM" were identified as such if pharmacists documented an adverse event during analysis of the medications' safety parameters that was compatible with those described in the Beers criteria (according to the "rationale" column present in Beers criteria tables). The most common negative clinical outcomes were described. For each PIM identified, it was also analyzed whether any pharmacist's intervention regarding its use was performed. These interventions were grouped according to the categories described in Table I.

These analyses (identification of "negative clinical outcomes potentially associated with PIM" and "pharmacists' interventions") were performed in pairs and independently by two CMM specialists. In case of disagreement between the peers, a third specialist was consulted, and a consensus was reached with the agreement of all three specialists after clinical discussion.

This study was approved by the ethics committee of the Federal University of Minas Gerais, Report

No. 25780314.4.0000.0149, and the secrecy of the participants' identity and confidentiality of information were guaranteed.

**TABLE I -** Type of pharmacists' interventions performed

| **Request of clinical/laboratory tests** |
|---|
| Suggestion of inclusion of additional drug therapy |
| Exchange for more appropriate or effective drug therapy |
| Modification of a pharmaceutical form |
| Dose increase |
| Dose reduction |
| Suggestion of use of drug therapy on-demand |
| Suspension of medication or drug tapering |
| Discussion of the case with a physician/ referrral to a physician |
| Provision of reminders or organization of medications to reinforce adherence |
| Request of prescription order to the physician to guarantee drug refill |
| Suggestion of medicine purchase to the patient |
| No intervention |

## RESULTS

### Step I

In total, 389 aged adults were included in the present study. They had a mean age of 70.3 years (minimum = 60, maximum = 98), and 52.4% of them (n = 204) were between 60-69 years of age. The majority were female (58.6%, n=228) and 63.8% presented 0-3 health problems (n = 248). Regarding the use of medications, 99% of the elderly used at least one drug (n = 385) and 51.2% used five or more medications (n = 199). The mean number of medications used was 4.8 (minimum = 0, maximum = 14) (Table II).

The prevalence of PIM use was 48.3% (95% CI 43.3–53.3). The number of PIMs used ranged from one to four, with the majority of the elderly using a single PIM (32.4%; n = 126). In total, 270 PIMs were identified during the initial consultations (14.5% of the total medications), and divided into 32 different types of PIM. The most used PIM were: omeprazole (n = 74, 27.4%), glyburide (n = 39, 14.4%), clonazepam (n = 26, 9.6%), and immediate release nifedipine (n = 23, 8.5%) (Table III). According to the intermediate groups proposed in the Beers Criteria, apart from immediate release nifedipine, the most common PIM groups used were: proton pump inhibitors (n = 77, 28.5%), benzodiazepines (n = 49, 18.1%), long-duration sulfonylureas (n = 39, 14.4%), and antidepressant agents (n = 13, 4.8%).

Table IV depicts the results of univariate and multivariate analyses of the characteristics associated with PIM use. According to the univariate analysis, PIM use was positively associated with the female sex, the presence of four or more health problems, and the use of five or more medications. Based on the multivariate analysis, only the use of five or more medications (OR 3.74; 95% CI 2.26–6.19) was found to be independently associated with the use of PIM.

**TABLE II -** Description of the older people population studied. Lagoa Santa, Minas Gerais, Brazil, 2015-2016. (n=389)

| ***Variables*** | ***n*** | ***%*** |
|---|---|---|
| *Age (years)* | | |
| 60-69 | 204 | 52,4 |
| 70-98 | 185 | 47,6 |
| *Sex* | | |
| Male | 161 | 41,4 |
| Female | 228 | 58,6 |
| *Number of health problems* | | |
| 0-3 | 248 | 63,8 |
| ≥4 | 141 | 36,2 |
| *Number of medicines* | | |
| 0-4 | 190 | 48,8 |
| ≥5 | 199 | 51,2 |

**TABLE III -** Frequency of potentially inappropriate medication (PIM) use among the older people population studied according to Beers Criteria during the initial evaluation. Lagoa Santa, Minas Gerais, Brazil, 2015-2016. (n=389)

| *PIM* | *n* | *%* |
|---|---|---|
| Omeprazole | 74 | 27.4 |
| Glyburide | 39 | 14.4 |
| Clonazepam | 26 | 9.6 |
| Nifedipine | 23 | 8.5 |
| Diazepam | 17 | 6.3 |
| Doxazosin | 13 | 4.8 |
| Amitriptyline | 11 | 4.1 |
| Ibuprofen | 9 | 3.3 |
| Digoxin | 7 | 2.6 |
| Risperidone | 5 | 1.9 |
| Methyldopa | 5 | 1.9 |
| Alprazolam | 4 | 1.5 |
| Amiodarone | 4 | 1.5 |
| Orphenadrine | 4 | 1.5 |
| Others | 29 | 10.7 |
| *Total* | *270* | *100* |

**TABLE IV –** Results from univariate and multivariate analysis of characteristics associated with the use of potentially inappropriate medications (PIM) use among the older people population studied during the initial evaluation. Lagoa Santa, Minas Gerais, Brazil, 2015-2016. (n=389)

| *Variables* | *PIM** | | *Univariate Analysis* | | *Multivariate Analysis* | |
|---|---|---|---|---|---|---|
| | *NO n (%)* | *YES n (%)* | *OR (95%CI)*** | *p-value**** | *OR (95%CI)*** | *p-value#* |
| *Age (years)* | | | | | | |
| 60-69 | 108 (52.9) | 96 (47.1) | 1.0 | - | 1.0 | - |
| 70-98 | 93 (50.3) | 92 (49.7) | 1.11 (0.75-1.66) | 0.599 | 1.10 (0.72-1.68) | 0.668 |
| *Sex* | | | | | | |
| Male | 97 (60.3) | 64 (39.7) | 1.0 | - | 1.0 | - |
| Female | 104 (45.6) | 124 (54.4) | 1.81 (1.20-2.72) | 0.004 | 1.53 (0.99-2.37) | 0.054 |
| *Number of health problems* | | | | | | |
| 0-3 | 145 (58.5) | 103 (41.5) | 1.0 | - | 1.00 | - |
| 4 or more | 56 (39.7) | 85 (60.3) | 2.14 (1.40-3.26) | 0.000 | 0.98 (0.58-1.65) | 0.935 |
| *Number of medicines* | | | | | | |
| 0-4 | 130 (68.4) | 60 (31.6) | 1.00 | - | 1.00 | - |
| 5 or more | 71 (35.7) | 128 (64.3) | 3.91 (2.56-5.95) | 0.000 | 3.74 (2.26-6.19) | 0.000 |

* Presence of at least one PIM identified in the first and/or second consultation

**Odds ratio (95%CI) estimated by logistic regression

*** Estimated by Pearson's chi-square

# Estimated by logistic regression; significant when < 0,05

### Step II

Of the total PIMs prescribed for the elderly (n = 270), two were not being used at the time of the first consultation (amiodarone and alprazolam) and their use was not reinforced by the pharmacist. For 21.3% (n = 57) of the other 268 PIMs being used, at least one potential negative clinical outcome was identified. For other 49 PIMs (18.3%), no negative outcome was documented. However, for the majority of PIMs (n = 162; 60.4%), it was not possible to evaluate the clinical outcomes due to lack of documentation or clinical/laboratorial tests (Table V).

The most common negative clinical outcome was hypotension (35.1% of the negative outcomes, n = 20), occurring with the use of doxazosin (n = 8), tricyclic antidepressants (n = 6), nifedipine (n = 4), and others (n = 2). The occurrence of fractures or diagnosis of osteoporosis among users of proton pump inhibitors was also frequent (21.1% of the negative outcomes, n = 11), and the duration of use of these agents ranged from 3 to 10 years. Another agent associated with fracture was orphenadrine (n = 1). Occurrence of hypoglycemia (14.0% of the negative outcomes) was identified among users of glyburide, and sedation was observed (10.5% of the negative outcomes) among users of psychotropic agents (benzodiazepines, n = 5; amitriptyline, n = 1) (Table V).

For most negative clinical outcomes, at least one pharmacist intervention was performed to mitigate the harm and/or discontinue PIM use (n = 45; 78.9% of potential negative clinical outcomes). These types of interventions (to suspend PIM or mitigate harm) were also the most frequent among the total number of interventions (performed for 64.2% of PIMs used, n = 172), with a special emphasis on suspension/medication tapering, and request of clinical/laboratory tests (40.7%, n = 109). However, for 32.1% of PIMs used (n = 86), there was no documentation of pharmacist intervention or DTPs identified. For the remaining PIMs (3.7%; n = 10), the pharmacists' interventions reinforced the use of the medication (Table VI).

**TABLE V -** Classification of potentially inappropriate medication (PIM) according to the presence of negative clinical outcome. Lagoa Santa**,** Minas Gerais, Brazil, 2015-2016. (n=389)

| ***PIM**** | ***n*** | ***%*** |
|---|---|---|
| *With lack of documentation or clinical/laboratorial tests* | *162* | *60.4* |
| *With potential negative clinical outcome* | *57* | *21.3* |
| Hypotension | 20 | 35.1 |
| Osteoporosis, bone diseases or fracture | 12 | 21.1 |
| Hypoglycemia | 8 | 14.0 |
| Sedation | 6 | 10.5 |
| Others | 11 | 19.3 |
| *With no potential negative clinical outcome* | *49* | *18.3* |
| *Total of PIMs used* | *268* | *100* |

**TABLE VI -** Pharmacist intervention performed for the potentially inappropriate medications (PIM). Lagoa Santa, Minas Gerais, Brazil, 2015-2016. (n=389)

| ***Type of Pharmacist Intervention*** | ***n*** | ***%*** |
|---|---|---|
| *To suspend PIM or mitigate adverse effects* | *172* | *64.2* |
| Suspension of medication or drug tapering | 61 | 22.8 |
| Request of clinical/laboratory tests | 48 | 17.9 |
| Discussion of the case with a physician/referral to a physician | 27 | 10.1 |
| Exchange for more appropriate/ effective drugs | 18 | 6.7 |
| Suggestion of use of drug therapy on-demand | 13 | 4.9 |
| Suggestion of additional drug therapy | 3 | 1.1 |
| Dose reduction | 2 | 0.7 |
| *Without pharmacist intervention* | *86* | *32.1* |
| *To reinforce PIM use* | *10* | *3.7* |
| Provision of reminders or organization of medications to reinforce adherence | 5 | 1.8 |
| Dose increase | 3 | 1.1 |
| Pharmaceutical form modification | 1 | 0.4 |
| Suggestion of additional therapy | 1 | 0.4 |
| *Total* | *268* | *100* |

## DISCUSSION

To our knowledge, there are no studies in the literature that have evaluated the clinical impact of the use of PIMs based on the updated Beers Criteria among older adults followed in a community CMM service. The high prevalence of PIM detected among community resident older patients in the present study (48.3%) is similar to that observed in another Brazilian study conducted in other two southeastern Brazilian cities (50.0% and 53,7%) (Novaes *et al*., 2017; Almeida *et al*., 2019) and in Kuwait 53,1%) (Awad, Hanna, 2019), that used the same version of Beers criteria. However, the prevalence found in our study is lower than that detected in South Korea (77.2%) (Kim, Lee, Kim, 2018) and Argentina (72,8%) (Chiapella *et al*., 2019); but higher than in Lithuania (24.1%) (Grina, Briedis, 2017) and among elderly people followed in an American CMM service (29%) (Patel, 2018), that also used the 2015 Beers criteria version. This demonstrates that even after considerable aging of the population and almost 30 years after the compilation of the first explicit PIM criteria, its use among older adult residents in the community is still high, which reinforces the need to establish more effective barriers to the prescription of such agents with potential risks.

Most PIMs can be replaced with safer alternatives and when this is not the case, the patient should be monitored by a health professional in order to prevent the occurrence of adverse effects (Hanlon, Semla, Schmader, 2015). However, PIM use without adequate therapeutic indication is usually common and its deprescription should be prioritized. For instance, longitudinal studies have continuously demonstrated the adverse effects associated with the prolonged use of proton pump inhibitors that were the most used PIM in the present study (James, Kumar, 2018; Pezeshkian, Conway, 2018; Freedberg, Kim, Yang, 2017; Savarino *et al*., 2017). The increased risk of dementia, *Clostridium difficile* infection, bone fractures and nutritional deficiencies among proton pump inhibitors pose a significant threat among older users (James, Kumar, 2018; Pezeshkian, Conway, 2018; Savarino *et al*., 2017). Therefore, initiatives have been taken to reduce their use, such as the elaboration of algorithms for their deprescription with strategies for suspension, tapering, or use on demand and should be put into practice specially among more frail patients (Farrell *et al*., 2017).

Similar to proton pump inhibitors, benzodiazepines, that were the second most prescribed PIM in the present study, also present risks associated with long-term use (e.g. cognitive impairment, increased mortality) as well as short-term use (e.g. sedation, delirium, falls, fractures) and are the focus of campaigns on rational deprescription (Huang *et al*., 2018; Pottie *et al*., 2018; Nascimento *et al*., 2017; AGS, 2015; Paterniti, Dufouil, Alperovitch, 2002). The use of benzodiazepines among the elderly is often documented in literature, especially for the management of anxiety and sleep disorders, although they are not indicated as the treatment of choice for such conditions (Filardi *et al*., 2017; Grina, Briedis, 2017; Novaes *et al*., 2017; Lader, 2014; Brunoni *et al*., 2013; Gisev *et al*., 2011; Spanemberg *et al*., 2011; Alvarenga *et al*., 2007). In all patients, especially in the elderly with signs and symptoms of anxiety and sleep disorders, non-pharmacological measures should be prioritized before considering medication treatment (Lader, 2014; Wennberg *et al*., 2013; Gisev *et al*., 2011; Spanemberg *et al*., 2011; Alvarenga *et al*., 2007). If medication treatment is required, the first-line treatment is the use of serotonin reuptake inhibitors (Lader, 2014; Wennberg *et al*., 2013; Gisev *et al*., 2011; Spanemberg *et al*., 2011; Alvarenga *et al*., 2007).

As in our study, Extavour & Perri (2016) also found a statistically significant association between the use of PIM and the number of medications used after multivariate analysis. A similar association was also detected in other studies with elderly community residents who used PIM according to the 2012 version of the Beers Criteria (Nascimento, Lima-Costa, Loyola Filho, 2016; Moriarty *et al*., 2015; Blanco-Reina *et al*., 2014; Nishtala *et al*., 2014). Thus, we reinforce the notion that polypharmacy is an important proxy for the use of PIM, being a relevant and practical screening tool for PIM use and for identifying older adults at high risk of developing adverse effects; therefore, polypharmy is also a good inclusion criteria for this population in CMM services (Nascimento, Lima-Costa, Loyola Filho, 2016).

A significant quantity of PIM led to the development of potential negative clinical outcomes (21.3%) with an emphasis on hypotension and hypoglycemia. These data

reinforce the need to reduce PIM prescription and provide safer geriatric pharmacotherapy. Most clinical outcomes involved the potential occurrence of falls and/or fractures (80,7% of the clinical outcomes involved either hypotension, osteoporosis, hypoglycemia or sedation), which is a major public health problem in the world that is frequently involves the use of fall-risk-increasing drugs and increased mortality (Hartholt *et al*., 2019; Seppala *et al*., 2018; De Vries *et al.,* 2018; AGS, 2015). Its prevention should, therefore, be one of the main focus in geriatric care.

Fall risk and other problems associated with the use of PIM can often be resolved by their replacement with safer agents available free of charge in the Brazilian health system, such as the safer sulfonylurea gliclazide, which may be prescribed instead of glyburide or safer antihypertensive agents (e.g. inhibitors of angiotensin-converting enzyme, thiazide diuretics) that can replace immediate-release alpha-adrenergic receptor antagonists or nifedipine (Brasil, 2017). These changes were some of the recommendations made by the pharmacists of the CMM service in this study, who proposed the suspension of PIM or actions that mitigated adverse effects for most negative clinical outcomes. This demonstrates the resolution of DTP associated with safety in this service, especially when pharmacists led an intervention for the major portion of negative outcomes (78,9%). However, a considerable proportion of PIM showed no documented safety parameter or absence of clinical/laboratorial tests (60.4%). It is likely that this percentage reflects, in part, the unavailability of updated monitoring parameters. This interpretation was reinforced by the high proportion of pharmacists' interventions involving the request for updated tests (17.9% of the interventions), mainly for the monitoring of glycated hemoglobin and blood pressure by means of residential measures.

It is believed that, unlike the findings of Maurício *et al*. (2016), among pharmacy students involved in a CMM service, the absence of documented safety parameters in this study can be the result of difficulties perceived by novice CMM pharmacists in comprehensively documenting the care process on a daily basis, and not from a lack of knowledge about PIM or tools for its detection. This perception is based on the fact that the pharmacists' interventions due to PIM use often involve a recommendation for withdrawal, exchange, use according to demand, dose reduction (35.1%), or discussion/referral to a physician for reassessment of the need for PIM (10.1%), even without associated negative clinical outcomes (71.5% of the interventions to suspend PIM or mitigate its adverse effects were performed in the absence of any negative clinical outcome - result not reported). This perception also corroborates with the low number of pharmacists' recommendations that reinforced the use of PIM (3.7%).

In addition, the types of pharmacists' interventions with a predominance of interventions to suspend PIM or minimize its adverse effects demonstrate that the approach of pharmacists to assess all of a patient's pharmacotherapy holistically, which is the foundation of the clinical performance in CMM services, has a high potential to reduce the use of PIM and the occurrence of its adverse clinical outcomes. However, due to the small number of consultations per patient, it was not possible to evaluate the effective deprescription of PIM, as shown by the study of Caffiero *et al*. (2017). In a systematic review, Viswanathan *et al*. (2015) also detected the positive impact of CMM on pharmacotherapy adequacy.

The present study presents as a limitation, the incompleteness of the documentation for some patient information at the time of CMM consultation, such as literacy, ethnicity, and occupation, which are factors that may be associated with PIM use. As mentioned before, documentation of safety parameters was also a limiting factor.

Another limitation was the fact that only the main Beers criteria list was applied, which led to the underestimation of the potential pharmacotherapeutic risks for older adults. Another fact that can lead to the underestimation of the potential pharmacotherapeutic risks is the use of the 2015 Beers criteria version at the time of the study instead of the last 2019 version recently published, since some medications added to this latest version are likely to be used in the study scenario (e.g.: glimepiride). Also, we must reinforce that, even though Beers criteria was chosen for this particular study, there are other lists than can be adopted to evaluate PIM use and should, therefore, be of knowledge of clinical pharmacists (Motter et al., 2018; Varallo et al., 2014). However, to our

knowledge, this is the first Brazilian study to evaluate the development of negative clinical outcomes and to assess pharmacist interventions regarding of PIM use. This demonstrates both the harmful effects of PIM and the potential of reducing their use with the provision of CMM services. The results of the prevalence and factors associated with PIM use in the present study corroborate with the findings of other studies, pointing to the use of multiple medications as potential proxy for PIM use and for patient referral to CMM services. In addition, the present study demonstrates the frequent occurrence of negative clinical outcomes that were identified by clinical pharmacists for most PIM used by the patients. This reinforces the need of a thorough pharmacotherapeutical evaluation to seek therapeutic alternatives or to mitigate their adverse effects, as proposed in most of the pharmacists' interventions assessed in the present study. Overall, our findings reinforce the potential of CMM services in improving the adequacy of geriatric pharmacotherapy and minimizing its risks. However, the present results are limited to this particular setting and may not be applicable to a different patient population.

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