International Journal of Clinical Pharmacy (2019) 41:913–919
https://doi.org/10.1007/s11096-019-00858-8

RESEARCH ARTICLE

Prevalence of potentially inappropriate medications in older adults in Argentina using Beers criteria and the IFAsPIAM List

Luciana C. Chiapella[1] · Jorgelina Montemarani Menna[2] · Marta Marzi[3] · María Eugenia Mamprin[1]

Received: 10 December 2018 / Accepted: 28 May 2019 / Published online: 3 June 2019

Abstract

Background Medications in which the risk of adverse events exceeds the expectations of clinical benefits are called potentially inappropriate medications (PIMs). To identify the use of PIMs in elderly patients, the most commonly used tool are the Beers criteria, developed for the population of the United States. Recently, a consensus panel of Argentine experts developed the first Latin American tool, called the IFAsPIAM List. *Objective* The present study aimed to identify PIM prescriptions in elderly outpatients, to estimate the prevalence of PIMs, and to evaluate their possible relation with polypharmacy and gender and age of the patients. Also, we aimed to compare the results obtained by using the Beers criteria and the IFAsPIAM List. *Setting* Ten community pharmacies of Rosario, Santa Fe, Argentina. *Methods* A cross-sectional observational study was conducted between February and September 2015. Data were acquired from 56,952 prescriptions prescribed to 2231 patients aged 65 years old or older. To detect the use of PIMs, we used two tools: the Beers criteria and the IFAsPIAM List. *Main outcome measure* The prevalence of PIM use according to the Beers criteria and the IFAsPIAM List. *Results* The monthly average of medications dispensed per patient was 4.35 ± 2.18 and 42.27% of the patients presented major polypharmacy. The prevalence of PIMs was 72.75% according to the Beers criteria and 71.13% according to the IFAsPIAM List (Kappa coefficient $k = 0.72$), and was significantly higher in patients with major polypharmacy, older than 75 years old, and females. The most frequent PIMs prescribed were anxiolytics, analgesics and antipsychotics. *Conclusions* The IFAsPIAM List is an effective tool to evaluate the prescription of PIMs in the elderly. The results showed a high prevalence of PIMs with a multicausal origin and directly associated with polypharmacy. As clarified by the authors of the IFAsPIAM List, the criteria specified in the list do not substitute the clinical evaluation of each patient.

Keywords Argentina · Beers criteria · Elderly · IFAsPIAM List · Potentially inappropriate medications

Impacts on practice

- Pharmacists information of inappropriate medications will help in reducing negative health outcomes in older persons and IFAsPIAM List constitutes a local Argentinian instrument that can be used routinely in pharmaceutical practice and contribute to better drug treatment in older adults.
- The IFAsPIAM List can be applied as a screening tool to identify potentially inappropriate medications. It can also be used for international comparisons of the prescription patterns of PIMs and may be used as a guide in clinical practice.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11096-019-00858-8) contains supplementary material, which is available to authorized users.

✉ María Eugenia Mamprin
mmamprin@fbioyf.unr.edu.ar

[1] Área Farmacología, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, CONICET, Rosario, Argentina

[2] Atención Primaria de la Salud, Ministerio de Salud de la Provincia de Santa Fe, Rosario, Argentina

[3] Área Matemática y Estadística, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Rosario, Santa Fe, Argentina

Introduction

The rapid growth of the elderly population (i.e. individuals aged 65 years or older) is a worldwide phenomenon that has triggered intense political and economic discussions [1]. In Argentina, in 2010, the Argentine elderly represented approximately 12.8% of the total population, whereas more recent data indicate that they now represent approximately 17.4% [2]. Elderly people are characterised by presenting age-related functional and cognitive impairment as well as many different diseases and physiological changes, all of which modify the pharmacodynamics and pharmacokinetics of drugs. Polypharmacy is defined as "the administration of several drugs simultaneously or administration of an excessive number of drugs" [3] and no consensus has been reached regarding the number of concomitant drugs required to achieve the designation of polypharmacy [4]. Polypharmacy is a growing and worrying phenomenon among older adults. In a recent study, we found that 47.1% of elderly outpatients that buy their prescribed medications in ten pharmacies, used five or more chronic drugs [5].

Potentially inappropriate medications (PIMs) in older people are drugs whose potential risks outweigh their desired benefits when more effective and safe therapeutic alternatives are available [6, 7]. Several tools have been developed to identify the use of PIMs in elderly patients, being the Beers criteria one of the most frequently used [8]. The latter criteria, which have been developed in the United States and have been updated several times, consist of a list of drugs that should be avoided in older people. These criteria may not necessarily need a review of the patients' medical records, since most of them are independent of the diagnoses [9]. However, the Beers criteria need to be adapted to the local situation in other countries. Lists of PIMs adapted to regional needs have been and are still being developed in various countries. In Europe, several adapted lists have been published in recent years [10–12] and, following this trend, in South America, the Brazilian Consensus on Potentially Inappropriate Medications for the older adults was published in 2016 [13]. In Argentina, by consensus of a panel of experts from the country, a list of potentially inappropriate active pharmaceutical ingredients (APIs) for use in older adults was generated using the Delphi technique [14]. This list of explicit criteria, called IFAsPIAM List, consists of 124 APIs and four API groups [15], allowing a better understanding of the site of action and the therapeutic indication for which they were considered inappropriate.

In a previous study [16], we identified a high prevalence of PIMs prescribed to elderly outpatients in Argentina according to the Beers criteria, as well as a high percentage of patients with polypharmacy [4]. However, studies on the prevalence of PIMs estimated by using tools developed in the local context have not yet been conducted.

Aim of the study

We aimed to identify prescriptions for PIMs in elderly outpatients in Argentina, to estimate the prevalence of PIMs, and to evaluate their possible relation with polypharmacy and gender and age of patients. Also, we aimed to compare the results of the use of the Beers criteria and the IFAsPIAM List.

Ethics approval

The study was approved by the Bioethics Committee of the School of Biochemical and Pharmaceutical Sciences of the Universidad Nacional de Rosario (Res. number 6060/228).

Methods

A cross-sectional observational study was conducted between February and September 2015. Data were acquired from 56,952 prescribed medications in ten pharmacies, dispensed to 2231 patients the Instituto Nacional de Seguridad Social para Jubilados y Pensionados (INSSJP), i.e. the National Institute of Social Services for Retirees and Pensioners, the Argentine public agency specialised in the care of the elderly aged 65 years old or older. The medications prescribed are included in the National Vademecum [17], an official permanently updated resource, in which all the medicines are published that are currently marketed in Argentina. Data recorded from each prescribed medication were: date of dispensing, drug name, dosage, route and number of packages dispensed, and gender and age of the patients. All individuals with prescriptions in three or more consecutive months were considered for the study and we verified which medication the patient used monthly during the study [5].

The dispensed medications were coded according to the Anatomical, Therapeutic, and Chemical (ATC-) classification version 2016 [15]. For each patient, the number of drugs dispensed monthly and the monthly average were determined. An average of one drug/month was considered monopharmacy, whereas a mean average of two to four drugs was considered minor polypharmacy, and a mean average of five or more drugs was considered major polypharmacy, according to the levels defined by Bjerrum et al. [4].

To detect the use of PIMs, we used two tools: the Beers criteria corresponding to the review published in 2015 [18] and the IFAsPIAM List [14]. Both tools contain a list of

medications that should be avoided or administered with caution regardless of the diagnosis or clinical condition of the patient. For the Beers criteria, we considered drugs not recommended for use in the elderly, with high and moderate quality of evidence and independence of diagnosis. We made a table, listing all Beers criteria used in this study, including modifications we made in order to adapt it to our data (see electronic supplement). Insulin was not considered; peripheral alpha-1 blockers were recommended to avoid in dosage > 4 mg/d; digoxin in dosage > 0.125 mg/d; antipsychotics first- and second-generation and non-cyclooxygenase-selective chronically used, and proton-pump inhibitors when used for > 8 week.

Each prescribed medicine was classified as PIM or not-PIM according to both tools. Then, each patient was classified as PIM user or PIM nonuser, according to whether he/she used at least one PIM according to the Beers criteria and/or the IFAsPIAM List. The concordance between both tools in the classification of prescribed medications and patients was measured by calculating Cohen's Kappa coefficient. This coefficient measures the agreement between two evaluators that classify each of the N elements in C mutually exclusive categories. In our case, each tool is considered an evaluator, each prescribed medication or each patient is an item and each of them is classified as PIM or non-PIM. We considered a good agreement if Cohen's Kappa coefficient was between 0.60 and 0.80.

The characteristics of patients and the medicine use were summarized by means of descriptive statistics. Quantitative variables were reported as means ± SDs, and categorical variables as proportions (%).

Pearson's Chi square test was used to analyse the possible relation between the use of PIMs and gender, age (65–74 years old—75 years old and older), and level of polypharmacy of the patients. If the association was statistically significant ($p < 0.05$), logistic regression was used to determine the odds ratio (OR) and confidence interval (95% CI). Statistical analysis was performed using Minitab v.17.

Results

The results showed that 1480 out of the 2231 patients (66.34%) were women. The age range was 65–101, with an average of 76.18 ± 7.31 years; 47.1% of these patients were between 65 and 74, and the remaining 52.9% were 75 years old or older.

One to fifteen drugs per patient were dispensed monthly, with an average of 4.35 ± 2.18 medicines. About 6.2% of the patients had monopharmacy, 51.6% had minor polypharmacy, and 42.3% had major polypharmacy.

Figure 1 shows the distribution of patients according to their age and level of polypharmacy. A statistically

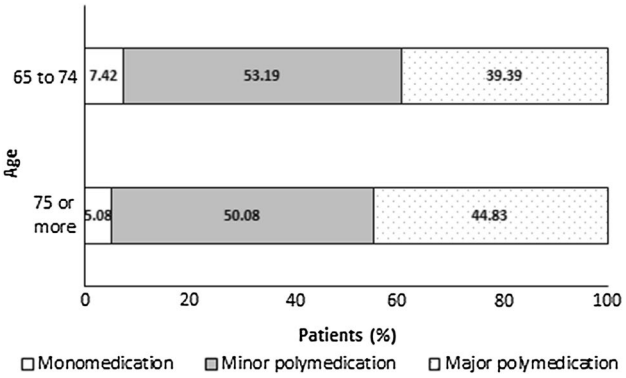

Fig. 1 Distribution of patients according to their age and level of polypharmacy

significant association was found between the level of polypharmacy and the age of the patients ($p = 0.007$), with a higher percentage of individuals with major polypharmacy observed among those aged 75 years old and older (< 75 years old: 39.39% vs. 75 years old or more: 44.83%).

The relationship between polypharmacy and the gender of the patients was also significant ($p = 0.008$). The prevalence of major polypharmacy was higher in women (females: 43.85% vs. males: 39.15%).

Both the use of the Beers criteria and the IFAsPIAM List disclosed a high prevalence of PIMs. According to the Beers criteria, 1623 patients (72.75%) received at least one PIM in the study period, whereas according to the IFAsPIAM List, 1587 individuals (71.13%) used some PIM. The concordance between the classification of patients based on both methods was good ($k = 0.72$).

When the Beers criteria were used, 11,626 (20.41%) prescribed medications were classified as PIMs, whereas when the IFAsPIAM List was used, 9295 prescribed medications (16.32%) were classified as PIMs. The agreement between the classification of the prescribed medications based on both methods was good ($k = 0.65$).

Table 1 shows the five pharmacological groups most frequently prescribed and the three APIs considered PIMs most frequently dispensed for each group, according to the use of the Beers criteria and the IFAsPIAM List. It can be observed that pharmacological groups most frequently prescribed found with both criteria were similar. Anxiolytics, non-steroidal anti-inflammatory drugs (NSAIDs), cardiovascular agents and antipsychotics were among the five pharmacological groups with the highest frequency of prescription detected by both methods. The remaining pharmacological group was the proton-pump inhibitors according to the Beers criteria and psychostimulants according to the IFAsPIAM List. According to the Beers criteria, 46.03% of patients used anxiolytics considered PIMs, 29.67% used proton-pump inhibitors considered PIMs and 22.37% used NSAIDs

Table 1 Most prescribed PIMs by ATc code-group

Beers criteria		IFAsPIAM List	
Pharmacological group (ATC code)—active pharmaceutical ingredient	Prescriptions *n* (%)	Pharmacological group (ATC code)—active pharmaceutical ingredient	Prescriptions *n* (%)
Anxiolytics (N05B)	4374 (7.68)	Anxiolytics (N05B)	4627 (8.12)
Alprazolam	2107 (3.70)	Alprazolam	2107 (3.70)
Clonazepam	1658 (2.91)	Clonazepam	1658 (2.91)
Lorazepam	527 (0.93)	Lorazepam	527 (0.93)
Proton-pump inhibitors (A02BC)	2926 (5.14)	NSAIDs (M01A)	1570 (2.76)
Pantoprazole	1236 (2.17)	Diclofenac	814 (1.43)
Omeprazole	1019 (1.79)	Meloxicam	548 (0.96)
Esomeprazole	330 (0.58)	Etoricoxib	144 (0.25)
NSAIDs (M01A)	1715 (3.01)	Cardiovascular system (C)	743 (1.30)
Diclofenac	814 (1.43)	Amiodarone	213 (0.37)
Meloxicam	548 (0.96)	Nifedipine	139 (0.24)
Ibuprofen	224 (0.39)	Digoxin	108 (0.19)
Antipsychotics (N05A)	854 (1.50)	Antipsychotics (N05A)	394 (0.69)
Quetiapine	434 (0.76)	Risperidone	245 (0.43)
Risperidone	245 (0.43)	Levomepromazine	87 (0.15)
Levomepromazine	87 (0.15)	Olanzapine	25 (0.04)
Cardiovascular system (C)	600 (1.05)	Psychostimulants and nootropics (N06B)	279 (0.49)
Amiodarone	213 (0.37)	Citicoline	208 (0.37)
Nifedipine	139 (0.24)	Idebenone	71 (0.12)
Digoxin	108 (0.19)		

NSAIDs non-steroidal anti-inflammatory drugs, *ATC code* anatomic therapeutic chemical code

considered PIMs. According to the IFAsPIAM List, 48.63% of the patients used anxiolytics considered PIMs, 20.22% used NSAIDs considered PIMs, and 7.80% used PIMs that act on the cardiovascular system.

Of all prescriptions analysed, we determined which APIs were considered PIMs by only one of the two tools here used (PIM for Beers and not for IFAsPIAM List or vice versa). Beers criteria consider proton-pump inhibitors, ibuprofen and naproxen as PIMs whereas the IFAsPIAM List does not. Indeed, 2926 prescriptions of proton-pump inhibitors, 224 of ibuprofen and 73 of naproxen were identified as PIMs using the Beers criteria but not by using the IFAsPIAM List. Another important difference is that the IFAsPIAM List considers opioids as PIMs, while the Beers criteria do not. There were 258 prescriptions of tramadol and 12 of buprenorphine, which are drugs that the Beers criteria do not consider as PIMs. In addition, the two criteria showed no agreement regarding paroxetine and fluoxetine, as well as regarding domperidone and cyclooxygenase 2 inhibitors (coxib). Finally, it is important to highlight that APIs with low therapeutic utility, such as citicoline and idebenone, were identified only through the use of the IFAsPIAM List.

Table 2 presents the characteristics of the patients according to whether they received at least one prescription of PIMs, considering each of the two tools used to identify them. Through the bivariate analysis, a statistically significant association was identified between the use of PIMs and the patient's age and gender and polypharmacy (Chi square test, $p < 0.05$ in all cases).

Subsequently, a multivariate logistic regression analysis was performed to determine the effect of the patients' characteristics on the possibility of receiving PIM prescriptions.

According to the classification made by the Beers criteria, the possibility of receiving PIMs was 1.63 times higher for women than for men (OR 1.63, 95% CI 1.33–2.00). Patients with major polypharmacy had a 3.42 times higher possibility of receiving PIMs than patients with minor polypharmacy (OR 3.42, 95% CI 2.73–4.29) and 13.77 times higher than patients with monopharmacy (OR 13.77, 95% CI 9.17–20.70). The association between PIM use and age was not statistically significant in the presence of the other variables.

According to the classification made by the IFAsPIAM List, the possibility of receiving PIMs was 1.72 times higher for women than for men (OR 1.72, 95% CI 1.41–2.09). Patients with major polypharmacy had a 2.79 times higher possibility of receiving PIMs than patients with minor polypharmacy (OR 2.79, 95% CI 2.26–3.46) and 9.23 times higher than patients with monopharmacy (OR 9.23, 95% CI 6.22–13.70). The possibility of receiving PIMs was

Table 2 Patients' characteristics according to potentially inappropriate medication (PIM) use and the tool used to identify them

Characteristics	Beers criteria		IFAsPIAM List	
	PIM users	PIM non-users	PIM users	PIM non-users
n	1623 (72.75%)	608 (27.25%)	1587 (71.13%)	644 (28.87%)
Age				
65–74	741 (45.65%)	310 (50.99%)	706 (44.49%)	345 (53.57%)
≥75	882 (54.35%)*	298 (49.01%)	881 (55.51%)*	299 (46.43%)
% Female	1131 (69.69%)*	349 (57.40%)	1114 (70.19%)*	366 (56.83%)
Monthly mean number of drugs				
2–4	759 (46.77%)	391 (64.31%)	747 (47.07%)	403 (62.58%)
≥5	820 (50.52%)*	123 (20.23%)	792 (49.91%)*	151 (23.45%)

*Chi square test, PIM users versus PIM non-users: $p < 0.05$

1.35 times higher for patients aged 75 years old or older, than for patients aged 65–74 (OR 1.35, 95% CI 1.16–1.64).

Discussion

This is the first study into PIMs that uses criteria agreed by Argentine experts and adapted to the local context, (the IFAsPIAM List). The prevalence of PIMs was found to be high, and similar according to both the Beers criteria (72.75%) and the IFAsPIAM List (71.13%). This prevalence was higher than that reported by other authors, who found a prevalence of PIM between 32% and 46% [1, 19–21], but similar to the results obtained by a study on the use of medications by institutionalized elderly patients in Argentina (80%) [22].

The high prevalence found may be due in part to the frequent precribing of benzodiazepines. Benzodiazepines are an essential pharmacological group in PIM detection strategies [23] and the higher prevalence observed in our study could be due to the overuse of alprazolam and clonazepam in our country [22, 24]. A high proportion of falls in older adults are related to the use of benzodiazepines, and the use of alprazolam in the 30 days before the fall has been found to significantly increase the likelihood of suffering a fall and to have a clinically relevant impact on the occurrence of these events [25].

Another group of interest in the elderly is NSAIDs. The prevalence of PIMs associated with these drugs is similar for the Beers criteria and the IFAsPIAM List (between 20 and 22%). A study conducted in outpatients of the Austral Hospital of Buenos Aires, Argentina, using the Beers criteria found a prevalence for the use of NSAIDs similar to ours [22].

One of the main differences found between the two tools used to identify the prescription of PIMs was that proton-pump inhibitors are not included in the IFAsPIAM List but were added to the 2015 version of the Beers criteria. Although the use of these drugs for more than 8 weeks has been associated with an increase in the risk of infections by *Clostridium difficile*, a reduction in the bone mineral density and an increase in the propensity to fractures, there is still no consensus regarding this association [21, 26].

It is important to note that, sometimes, pain in the elderly is not treated by drugs of the first step of the World Health Organization analgesic ladder [27] and that opioids are usually used in the treatment of moderate-severe pain and neuropathic pain. However, there is no clear evidence that they can be used safely in the elderly. Tramadol, for example, is not included in the Beers criteria but is considered a PIM in the IFAsPIAM List, the EU (7)-PIM list and the Brazilian list, but only in cases where the patient has chronic constipation [12, 13]. These differences show that these lists should be revised and permanently updated because new drugs are coming on the the market while others are withdrawn, and because future publications could provide new information about the safety of available drugs and clinical implications of their use in the elderly. Another aspect to consider is that the level of evidence used in the creation of lists of PIMs using the Delphi technique is generally based on published randomised and controlled trials; however, older people have low enrolment in clinical trials [28].

An interesting finding when using the IFAsPIAM List was that it identified drugs whose therapeutic efficacy has not been proven, such as idebenone and citicoline. In the United States, these substances are marketed only as a dietary supplement because there is not enough evidence to rate their effectiveness in Alzheimer's disease or other types of dementia. In some European countries, idebenone is used only to treat visual impairment in adults and adolescents with Leber's hereditary optic neuropathy [29, 30]. But in Argentina, idebenone and citicoline are classified as nootropic drugs (N06B ATC classification) and marketed as medicines for the treatment of mild and moderate cognitive disorders in patients with dementia. Many authors consider the use of these drugs as an indicator of

low prescribing quality and that these drugs contribute to polypharmacy and generate unjustified expenses for both the patient and the health system [31].

The advantages of using local criteria for the identification of PIMs include the possibility of detecting specific for pharmaceutical formulations marketed in Argentina as PIMs, that other countries have withdrawn from the market. Such is for instance the case with domperidone, with 227 prescriptions recorded in this study. In the United States, domperidone has been removed from the market because it increases the risk of ventricular arrhythmia and sudden cardiac death [32].

The identification of factors associated with PIM use is essential to prioritize actions that can optimize prescribing, as well as to design, develop and implement effective health practices aimed at promoting the safe use of medicines in the elderly. A statistically significant association was found between polypharmacy and PIM use, a fact that has also been described by other authors [19, 33, 34]. Some authors claim that the concomitant use of more than four drugs significantly increases the risk of underuse of some drugs, the use of PIMs and the adverse reactions associated with drugs [35, 36].

This study has some limitations, such as: (1) the fact that register-based studies can only report drug prescription and delivery patterns, and merely assume that these adequately reflect the actual use of drugs by patients (given that adherence to treatments may vary); (2) that the lack of information on drugs used in selfmedication may have led to an underestimation of the frequency of PIM use, since this is a frequent practice among older adults [37]; and (3) that we had no information about the clinical conditions associated with the use of PIMs. Despite these limitations, this is the first study that evaluates inappropriate medication by comparing a local tool such as the IFAsPIAM List with the Beers Criteria and the results may be useful to reconsider the prescription of certain drugs in elderly patients [38].

Conclusions

Argentina currently has a list of explicit criteria for the identification of medications (the IFAsPIAM List) that, could be inappropriate in older adults, due to their unfavourable benefit-risk profile. The results from this study show that the IFAsPIAM List is an effective tool to evaluate the prescription of PIMs in the elderly. The IFAsPIAM List was compared with the internationally used Beers criteria. The results showed a high prevalence of PIMs with a multicausal origin and directly associated with polypharmacy. But as stressed by the authors of the IFAsPIAM List, the criteria specified in the list do not substitute the clinical evaluation of each patient.

Funding This study was supported by Universidad Nacional de Rosario (No. 445/2015) and a grant from Secretaría de Estado de Ciencia, Tecnología e Innovación-SECTEI-(No. 2010-174-14), Santa Fe, Argentina.

Conflicts of interest The authors report no conflict of interest in the conduction of this study or the preparation of this manuscript.

References

1. Pandraud-Riguet I, Bonnet-Zamponi D, Bourcier E, Buyse M, Laribe-Caget S, Frémont P, et al. Monitoring of potentially inappropriate prescriptions in older inpatients: a French multicenter study. J Am Geriatr Soc. 2017;65(12):2713–9.
2. IDELAS-UCES. La población argentina aumentó su edad promedio respecto de la media del mundo. In: Boletín Mensual IDELAS. http://la5pata.com/2017/02/09/idelas-uces-la-poblacion-argentina-aumento-su-edad-promedio/. Accessed 1 Dec 2018.
3. World Health Organization. A glossary of terms for community health care and services for older persons. WHO Centre for Health Development; 2004.
4. Bjerrum L, Rosholm JU, Hallas J, Kragstrup J. Methods for estimating the occurrence of polypharmacy by means of a prescription database. Eur J Clin Pharmacol. 1997;53(1):7–11.
5. Chiapella LC, Montemarani Menna J, Mamprin ME. Assessment of polypharmacy in elderly patients by using data from dispensed medications in community pharmacies: analysis of results by using different methods of estimation. Int J Clin Pharm. 2018. https://doi.org/10.1007/s11096-018-0663-3.
6. Fick DM, Mion LC, Beers MH, Waller JL. Health outcomes associated with potentially inappropriate medication use in older adults. Res Nurs Health. 2008;31(1):42–51.
7. Laroche ML, Charmes JP, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? Br J Clin Pharmacol. 2007;63(2):177–86.
8. Campanelli CM. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60(4):616–31.
9. Steinman MA, Beizer JL, DuBeau CE, Laird RD, Lundebjerg NE, Mulhausen P. How to use the American Geriatrics Society 2015 Beers Criteria—a guide for patients, clinicians, health systems, and payors. J Am Geriatr Soc. 2015;63(12):e1–7.
10. Holt S, Schmiedl S, Thurmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arzteblatt Int. 2010;107(31–32):543–51.
11. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213–8.
12. Renom-Guiteras A, Meyer G, Thürmann PA. The EU (7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015;71(7):861–75.
13. Oliveira M, Amorim W, Oliveira C, Coqueiro H, Gusmão L, Passos L. Consenso brasileiro de medicamentos potencialmente inapropriados para idosos. Geriatr Gerontol Aging. 2016;10(4):168–81.
14. Marzi MM, Pires MS, Quaglia NB. Ingredientes Farmaceuticos Activos Potencialmente Inapropiados en Adultos Mayores: Lista IFAsPIAM: Panel de Consenso Argentino. Value Health Reg Issues. 2018;17:38–55.

15. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2016. 19 ed. Oslo, Norway: 2015.
16. Chiapella LC, Montemarani Menna J, Mamprin ME. Potentially inappropriate medications in elderly ambulatory patients: a comparative study between a primary health care center and a community pharmacy. Value Health Reg Issues. 2018;17:119–25.
17. Anmat. Vademecum Nacional de Medicamentos. http://anmatvademecum.servicios.pami.org.ar/. Accessed 1 Dec 2018.
18. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American geriatrics society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227–46.
19. Holmes HM, Luo R, Kuo YF, Baillargeon J, Goodwin JS. Association of potentially inappropriate medication use with patient and prescriber characteristics in Medicare Part D. Pharmacoepidemiol Drug Saf. 2013;22(7):728–34.
20. Lopes LM, Figueiredo TP, Costa SC, Reis AM. Use of potentially inappropriate medications by the elderly at home. Ciencia saude coletiva. 2016;21(11):3429–38.
21. Cano JP, García AA, Cánovas JJG, Ruiz JFS, Rausell VJR, Soto MT. Prescripción potencialmente inadecuada en mayores de 65 años según los criterios de Beers originales y su versión adaptada. Atención Primaria. 2018;50(2):106–13.
22. Fajreldines A, Insua J, Schnitzler E. Prevalencia de prescripcion potencialmente inapropiada de medicamentos en adultos mayores. Revista de calidad asistencial: organo de la Sociedad Espanola de Calidad Asistencial. 2016;31(5):279–84.
23. Chang CM, Liu PYY, Yang YHK, Yang YC, Wu CF, Lu FH. Use of the Beers criteria to predict adverse drug reactions among first-visit elderly outpatients. Pharmacotherapy. 2005;25(6):831–8.
24. Bertoldo P, Beltramo A, Rimoldi E, Bertoldo J, Vidaurre M, Valenciaga M, et al. Patrones de prescripción de benzodiacepinas, antidepresivos e hipnóticos en diferentes ciudades de Argentina. Rev AAFH. 2018;5(1):4–15.
25. Díaz-Gutiérrez MJ, Martinez-Cengotitabengoa M, de Adana ES, Cano AI, Martínez-Cengotitabengoa MT, Besga A, et al. Relationship between the use of benzodiazepines and falls in older adults: a systematic review. Maturitas. 2017;101:17–22.
26. Thaler HW, Sterke C, Van Der Cammen TJ. Association of proton pump inhibitor use with recurrent falls and risk of fractures in older women: a study of medication use in older fallers. J Nutr Health Aging. 2016;20(1):77–81.
27. World Health Organization. WHO's pain ladder. 2011. http://www.who.int/cancer/palliative/painladder/en. Accessed 2 Dec 2018.
28. Campbell S, Cantrill J. Consensus methods in prescribing research. J Clin Pharm Ther. 2001;26(1):5–14.
29. Weyer G, Babej-Dölle R, Hadler D, Hofmann S, Herrmann W. A controlled study of 2 doses of idebenone in the treatment of Alzheimer's disease. Neuropsychobiology. 1997;36(2):73–82.
30. Mariotti C, Solari A, Torta D, Marano L, Fiorentini C, Di Donato S. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. Neurology. 2003;60(10):1676–9.
31. Gómez V, Armesto J, Calvo M, Candás M, Fidalgo S, Rigeira A. Utilidad terapéutica de los medicamentos financiados por el Sistema Nacional de Salud. Madrid: INSALUD; 2001.
32. Makari J, Cameron K, Battistella M. Domperidone-associated sudden cardiac death in the general population and implications for use in patients undergoing hemodialysis: a literature review. Can J Hosp Pharm. 2014;67(6):441.
33. Cooper JA, Moriarty F, Ryan C, Smith SM, Bennett K, Fahey T, et al. Potentially inappropriate prescribing in two populations with differing socio-economic profiles: a cross-sectional database study using the PROMPT criteria. Eur J Clin Pharmacol. 2016;72(5):583–91.
34. Chang CB, Yang SY, Lai HY, Wu RS, Liu HC, Hsu HY, et al. Application of three different sets of explicit criteria for assessing inappropriate prescribing in older patients: a nationwide prevalence study of ambulatory care visits in Taiwan. BMJ Open. 2015;5(11):e008214.
35. Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. J Am Acad Nurse Pract. 2005;17(4):123–32.
36. Cojutti P, Arnoldo L, Cattani G, Brusaferro S, Pea F. Polytherapy and the risk of potentially inappropriate prescriptions (PIPs) among elderly and very elderly patients in three different settings (hospital, community, long-term care facilities) of the Friuli Venezia Giulia region, Italy: are the very elderly at higher risk of PIPs? Pharmacoepidemiol Drug Saf. 2016;25(9):1070–8.
37. Chui MA, Stone JA, Holden RJ. Improving over-the-counter medication safety for older adults: a study protocol for a demonstration and dissemination study. Res Soc Adm Pharm. 2017;13(5):930–7.
38. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72–83.