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ORIGINAL ARTICLE

Geriatrics, Gerontology and Aging

Medication package inserts do not present adequate information on potential risks for older adults in Brazil

Bulas de medicamentos não apresentam informações adequadas sobre potenciais riscos para idosos no Brasil

Vinícius Augusto Andrade Freitas[a], **Sharlene Lopes Pereira**[b]

[a] Medical School, Universidade Federal de Juiz de Fora – Juiz de Fora (MG), Brasil.
[b] Departament of Pharmacology, Institute of Biological Sciences, Universidade Federal de Juiz de Fora – Juiz de Fora (MG), Brasil.

Correspondence data
Sharlene Lopes Pereira – Rua José Lourenço Kelmer, s/n. – São Pedro – CEP 36036-900 – Juiz de Fora (MG), Brasil. E-mail: sharlene.pereira@ufjf.br

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Abstract

Objective: To compare information on the risks of potentially inappropriate medications (PIMs) for older adults in the Beers criteria with data in the package inserts made available by the Brazilian Health Regulatory Agency.

Methods: This is an observational, cross-sectional study that compared information on the package inserts of 33 brand-name drugs in the Brazilian market with specific recommendations for older adults contemplated in the Beers criteria, categorizing them into: complete, incomplete, absent, or discrepant.

Results: Among the analyzed package inserts, 21.21% did not present a specific section dedicated to the use of these drugs by older adults and data were scattered throughout the text; 63.64% were classified as incomplete; 33.33% lacked data; and 3.03% had discrepant information.

Conclusion: The analyzed package inserts presented incomplete data or lacked information characterizing the drugs as PIMs for older adults. This study demonstrated that some package inserts of drugs used in Brazil are not satisfactory, warranting higher caution in the medical community when prescribing these medications and guiding patients.

Keywords: inappropriate prescribing; potentially inappropriate medication list; medicine package inserts; drug-related side effects and adverse reactions.

Resumo

Objetivo: Comparar as informações sobre os riscos de medicamentos potencialmente inapropriados (MPIs) para idosos contidas nos critérios Beers com as informações presentes nas bulas para profissionais de saúde disponibilizadas pela Agência Nacional de Vigilância Sanitária no Brasil.

Metodologia: Estudo observacional e transversal que comparou informações das bulas para profissionais de saúde de 33 medicamentos de referência no mercado brasileiro com recomendações específicas para idosos contempladas nos critérios Beers e que foram categorizadas em: completas, incompletas, ausentes ou discrepantes.

Resultados: Dentre as bulas dos MPIs analisadas, 21,21% não apresentam seção específica destinada ao uso desses medicamentos por idosos, nas quais as informações estão dispersas pelo texto; 63,64% delas foram classificadas como incompletas; 33,33% tinham informações ausentes; e 3,03% com informações discrepantes.

Conclusão: As bulas analisadas apresentaram dados incompletos ou não apresentam qualquer informação que caracterizasse o medicamento como MPI para idosos. Este estudo demonstra que algumas bulas de medicamentos utilizados no Brasil não estão satisfatórias, sugerindo maior cautela à comunidade médica na prescrição e na orientação aos seus pacientes.

Palavras-chave: prescrição inadequada; lista de medicamentos potencialmente inapropriados; bulas de medicamentos; efeitos colaterais e reações adversas relacionados a medicamentos.

INTRODUCTION

The older population in Brazil has surpassed 30 million inhabitants in 2017, encompassing around 14% of the country's citizens according to the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística [IBGE]).[1] Considering the current and accelerated demographic transition process, relevant clinical characteristics of the geriatric age group are commonly neglected, leading to higher risks for these individuals. In this scenario, it should be noted that 85% of older adults present a chronic disease and 10% of them present five or more comorbidities.[2] Therefore, considering the fast-paced growth of this population and their higher illness rates, around two-thirds of the country's medications are prescribed to older adults.[3]

Various physiological alterations that happen in older adults and influence pharmacokinetics and pharmacodynamics[4,5] led to the need to propose restrictions on prescriptions for this population, with the creation of groups of potentially inappropriate medications (PIMs) for older adults. PIMs correspond to pharmacological groups that present a high risk of adverse reactions due to inappropriate posology, interactions, or indications, when there is evidence of an alternative with similar or higher effectiveness at a lower risk.[6] The classification of a drug as a PIM, in any circumstance or considering specific interactions and posology, is defined by standards such as the Beers criteria, whose most recent version was published in 2019 by the American Geriatrics Society (AGS).[7] These criteria have contributed to the quality and safety of prescriptions for older adults.[8] They are recognized in Brazil and worldwide, providing access to knowledge on the use of medications in the population over 60 years old in a practical way in order to contribute to the medical education process and promote better health care to the geriatric population. Recommendations made by these criteria synthesize scientific evidence for decision-making, suggesting rational considerations on cost-benefit and monitoring, also serving as a tool to help in the detection of undesirable effects.[9]

In spite of tools such as the Beers criteria and the association between the use of PIMs and increased hospitalizations and mortality among older adults, inappropriate prescribing is still very frequent. Understanding the potential risks of the use of PIMs by the geriatric population, this study compared the guidance and warnings on the use of these drugs by older adults described by the 2019 Beers criteria and the information presented at medication package inserts made available by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária [ANVISA]) in Brazil.

METHODS

This documental study analyzed electronic prescription information on PIMs made available by ANVISA through the website: https://consultas.anvisa.gov.br/#/bulario/. This information was compared with the respective data presented at the 2019 Beers criteria.[7]

The following groups of PIMs present in the criteria were selected for the study: NSAIDs, benzodiazepines, antidepressants, Z-drugs, antipsychotics, antiulcer drugs, antidiabetic drugs, and muscle relaxants. In this study, we did not analyze the prescribing information on cardiovascular PIMs, as the package inserts of these drugs have been contemplated by a recent analysis.[8]

Among the mentioned PIM groups, 33 brand-name drugs with broad clinical use in Brazil and with active registration at ANVISA were selected for evaluation. We analyzed the information contained in the electronic prescribing information. When available at the ANVISA record, package inserts were accessed via the "ProDoctor Medicamentos" app.

After selecting medications, the presence or absence of a specific section dedicated to older adults was identified in each package insert. This specific section could have the title "Use in older adults," or "Use in the geriatric population," for example.

Information on the use of these PIMs by older adults contained in the package inserts was compared with the respective data contemplated by the 2019 Beers criteria.[7] Data were then categorized as: complete, incomplete, absent, or discrepant. Data were considered incomplete when any of the reasons for the medication to be considered a PIM (according to the mentioned criteria) was not found in the respective package insert. When none of the reasons was found in the medication package insert, the information was considered absent. When the package insert presented data that were contrary to those contained in the Beers criteria for the same PIM, they were considered discrepant.

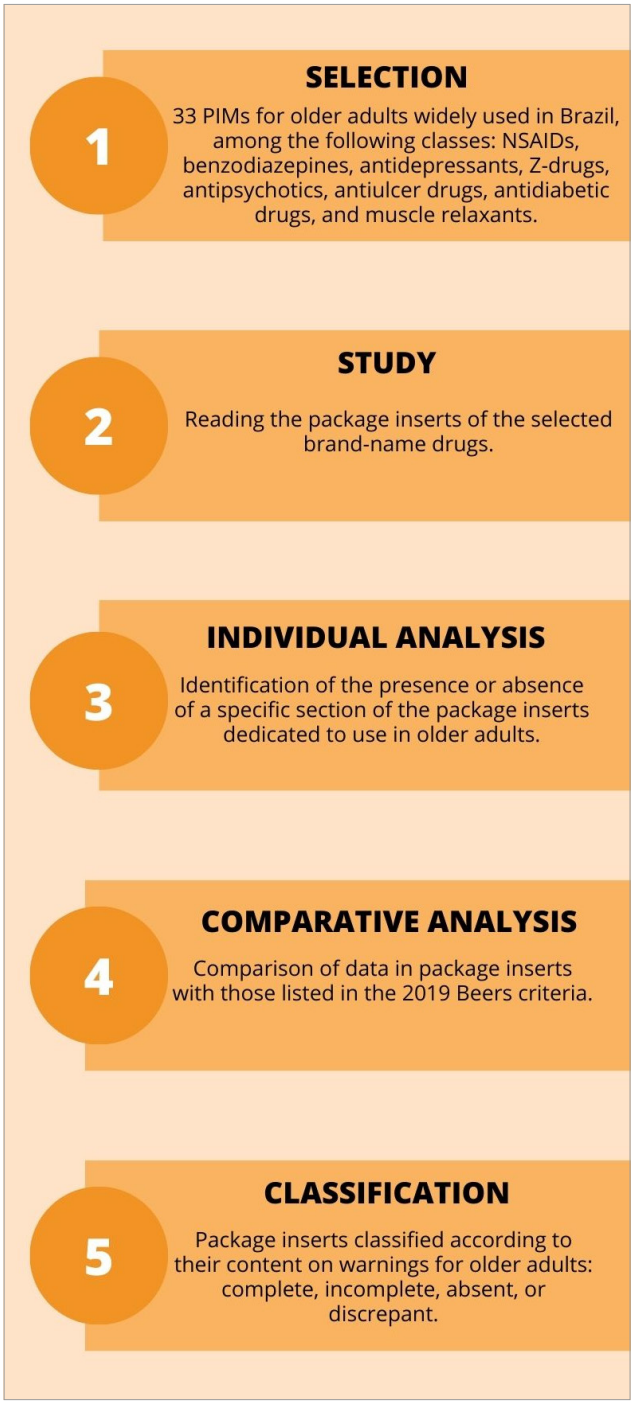
A Google Sheets spreadsheet was built for organizing all the collected data and for the comparative analysis and inclusion of suggestions for complementing the prescribing information on the evaluated PIMs. The methodology used in this study has been briefly described in Figure 1.

RESULTS

Out of the analyzed package inserts, seven (21.21%) did not present a specific section dedicated to the use of these drugs by older adults, that is, data were scattered throughout the document and not highlighted in a section titled "Use in older adults" or "Use in the geriatric population." These

package inserts were for the following drugs: alprazolam, piroxicam, ibuprofen, chlorpromazine, levomepromazine, zaleplon, and glimepiride.

The package inserts of drugs acting on the central nervous system such as benzodiazepines, Z-drugs, and muscle relaxants were incomplete or did not present information on risks for older adults (Table 1). The analyzed package inserts of antidepressants and antipsychotics were also incomplete or without any warning regarding older adults as mentioned in the Beers criteria (Table 2). The prescribing information on PIMs of great clinical importance such as antiulcer drugs, antidiabetic drugs, and NSAIDs also presented incomplete or absent data, and one of them (glimepiride) presented discrepant or contradicting data in comparison with the mentioned criteria (Table 3).



*PIMs: potentially inappropriate medications; NSAIDS: nonsteroidal anti-inflammatory drugs.

FIGURE 1. Methodology used for evaluating package inserts of potentially inappropriate medications for older adults.

The analysis of the package inserts of the selected PIMs showed that 63.64% (n = 21) were incomplete, 11 (33.33%) lacked data, and one (3.03%) had discrepant information. None of the package inserts presented complete information.

DISCUSSION

This study, performed with the package inserts of Brazilian medications, identified that none of the analyzed documents presented complete data on the effects of PIMs in older adults, even though the relevance of educating health professionals on the physiological changes in older adults for adequately prescribing drugs to the geriatric population is well established.[10] This reinforces the importance of widely promoting the Beers criteria[7] among geriatricians and other prescribers.

Studies have shown that package inserts do not provide adequate information to patients and prescribers. In 2002, directive SVS No. 110/1997 of the Secretariat of Health Surveillance of the Ministry of Health (Secretaria de Vigilância Sanitária do Ministério da Saúde [SVS/MS]), which regulates the creation of package inserts in Brazil, was used as reference by Gonçalves et al.[11] for evaluating 168 package inserts. In this study, 91.40% of the documents were considered unsatisfactory when considering "patient information," 97.00% were considered unsatisfactory regarding "technical information," and 86.00% did not present data on use in older patients. More recently, Marques et al.[8] analyzed precautions for the use of cardiovascular drugs in older adults present in package inserts, using the 2016 Brazilian Consensus on Potentially Inappropriate Medications for Older Adults[12] as a parameter, and noticed that 40.00% of the analyzed documents did not contain guidance or warnings dedicated to the older population or presented discrepant information when compared to the Brazilian Consensus. Studies performed in other countries also noticed a lack of important information in medication package inserts. A study in Iran[13] evaluated the quality of 100 package inserts of the most commercialized medications in the country according to criterium by the Iran Food and Drug Administration (IFDA), which follows

guidance by the American Food and Drug Administration (FDA). None of the evaluated package inserts presented all the criteria requested by IFDA and only 12.70% presented remarks on the geriatric population. Al-Aqeel[14] analyzed 60 package inserts of a list of best-selling drugs in Saudi Arabia produced by different laboratories. Only 18 documents (30.00%) presented information on use in older adults. Govindadas et al.[15] evaluated 263 package inserts in south India, according to their regulatory standards, and concluded that none of them were complete when considering the analyzed criteria. The study evaluated descriptions about medication use in vulnerable populations such as pregnant and lactating women, but it did not evaluate content on the older population. Qatmosh et al.[16] analyzed and compared 35 package inserts of antihypertensives produced locally in Palestine and their imported analogs. None of them fulfilled the 31 analyzed criteria nor presented remarks on the geriatric population. Overall, international analyses corroborate our study, indicating a low quality of package inserts both considering general issues and restrictions directed to special groups such as the older population.

The Brazilian Consensus on Potentially Inappropriate Medications for Older Adults, published in 2016, validated the content of the 2012 Beers and 2006 Stopp criteria in the Brazilian population. This consensus validated 43 criteria for medications that should be avoided in older adults regardless of the clinical condition and 75 criteria that depended on their clinical condition.[12] As the 2016 Brazilian Consensus was based in outdated criteria when compared to the 2019 Beers criteria, this study adopted the latter as a parameter for evaluating the content of package inserts. The Brazilian Consensus should be updated according to the 2019 Beers criteria.

In this study, most of the package inserts (two-thirds) were classified as incomplete regarding the description of PIM effects in older adults. Prescribing information on zolpidem, for example, is incomplete as to the information characterizing it as a PIM for older adults, such as a higher risk of falls, fractures, and traffic accidents, as indicated by the Beers criteria.[7] The same thing happened with the package insert of benzodiazepines, and these are pharmacological groups frequently and often inappropriately used by the geriatric age group. Package inserts for this group should be revised, especially those without information on the geriatric population such as clonazepam, lorazepam, and alprazolam. Regulatory authorities and the pharmaceutical industry must include information on the increased risk of overdose in case of concomitant use with drugs acting on the central nervous system, in addition to a warning about the risk of cognitive impairment, delirium, falls, fractures, and traffic accidents, especially with long-term use. A study performed in long-term care facilities in the city of Natal (RN) showed that 54.60% of older adults used PIMs, of which benzodiazepines were

TABLE 1. Comparison of information on the use of benzodiazepines, Z-drugs, and muscle relaxants by older adults present in professional package inserts and the 2019 Beers criteria.

PIM	Beers 2019	Medication package insert	Comparative analysis	Complementation of package insert
Benzodiazepines				
Alprazolam	Higher risk of cognitive impairment, delirium, falls, fractures, and traffic accidents	Use the minimum effective dose for older adults	Absent data	Higher risk of cognitive impairment, delirium, falls, fractures, and traffic accidents
Lorazepam Clonazepam		Paradoxical reactions, use the minimum effective dose		
Diazepam		Paradoxical reactions, slow elimination, lower doses, and higher monitoring. Higher risk of falls and fractures	Incomplete data	Risk of cognitive decline, delirium, and traffic accidents
Z-drugs				
Zolpidem	Higher risk of delirium, falls, fractures, and traffic accidents	Amnesia and delirium are possible adverse effects.	Incomplete data	Higher risk of falls, fractures, and traffic accidents
Zaleplon		Older adults are more susceptible to behavioral adverse effects	Absent data	Higher risk of delirium, falls, fractures, and traffic accidents
Muscle relaxants				
Carisoprodol	Anticholinergic effects, sedation, and higher risk of falls and fractures	High risk of gastrointestinal adverse effects and respiratory depression	Incomplete data	Higher risk of anticholinergic effects, sedation, falls, and fractures
Cyclobenzaprine		Start at a low dose and gradually increase it	Absent data	

PIM: potentially inappropriate medication; anticholinergic effects: constipation, dry mouth, urinary retention, blurred vision.

one of the main groups; this was associated with increased hospitalizations, deaths, and health costs.[17] Moreover, a more recent study performed at Hospital Universitário da Universidade Federal de Juiz de Fora (HU-UFJF), in Juiz de Fora (MG), evaluated 187 medical records of hospitalized older patients and revealed a high prevalence of the use of PIMs, among which benzodiazepines and omeprazole were the most prevalent.[18]

Self-medication is a frequent practice and constitutes an important factor for the use of PIMs, especially NSAIDs, muscle relaxants, and painkillers.[19] Considering that self-medication is frequent in older adults, especially considering NSAIDs, muscle relaxants, and painkillers,[19] it is crucial that package inserts for these drugs contain information on the risks of their use in this population. Conversely, in this study, all the evaluated NSAID package inserts presented incomplete or

TABLE 2. Comparison of information on the use of antidepressants and antipsychotics by older adults present in professional package inserts and the 2019 Beers criteria.

PIM	Beers 2019	Medication package insert	Comparative analysis	Complementation of package insert
Antidepressants				
Amitriptyline	Anticholinergic effects, sedation, orthostatic hypotension, and higher risk of falls and fractures	Lower doses due to higher sensitivity	Absent data	Higher risk of anticholinergic effects, sedation, orthostatic hypotension, falls, and fractures
Nortriptyline		Lower doses and cardiovascular monitoring. Risk of confusion		
Paroxetine		Dose up to 40 mg/day		
Clomipramine		Risk of paralytic ileus (anticholinergic effect). Monitor ECG		Risk of other anticholinergic effects, orthostatic hypotension, sedation, falls, and fractures
Imipramine		Caution and low doses. Higher risk of anticholinergic effects (paralytic ileus), neurologic effects, cardiovascular effects (orthostatic hypotension), and bone fractures. Monitor cardiac function	Incomplete data	Risk of other anticholinergic effects, sedation, and falls
Antipsychotics				
Haloperidol	Avoid long-term use in older adults, except in case of schizophrenia or bipolar disorder. Higher risk of stroke and higher cognitive decline and mortality rates in older adults with dementia. High rate of physical dependence, tolerance, and overdose	Higher risk of stroke and higher mortality rate in older adults with dementia		Higher risk of cognitive decline in older adults with dementia. High rate of physical dependence, tolerance, and overdose
Risperidone				
Chlorpromazine		Higher risk of stroke, higher mortality rate in older adults with dementia, sedation, and hypotension		
Levomepromazine				
Olanzapine		Increased risk of stroke. Abnormal gait and falls are very frequent		Higher risk of cognitive decline and mortality in older adults with dementia. High rate of physical dependence, tolerance, and overdose
Thioridazine		Alterations in cardiac conduction. Higher risk of cognitive decline in cases of dementia. Higher risk of fractures due to sedation and postural hypotension		Higher risk of stroke and mortality in older adults with dementia. High rate of physical dependence, tolerance, and overdose
Quetiapine		High risk of tardive dyskinesia with long-term use. Use with caution at the lowest tolerable dose. Not approved for older adults with dementia		Higher risk of stroke, cognitive decline, and mortality in older adults with dementia. High rate of physical dependence, tolerance, and overdose

PIM: potentially inappropriate medication; anticholinergic effects: constipation, dry mouth, urinary retention, blurred vision; ECG: electrocardiogram.

absent data on their use in older adults. For example, some of the package inserts did not even mention the possibility of increased arterial pressure and/or kidney injury.[7]

Patient and professional package inserts should contribute to rational use of the pharmaceutical product by reinforcing the instructions received at the moment of prescription and increasing treatment adherence. The content and format of package inserts are important for patient comprehension, which influences a reduction in self-medication and adverse events.[20] In recent years, studies on the comprehension of package inserts[20] and analyses of better practices for optimizing the prescription given to patients[21] have suggested the importance of retrieving these data for increasing adherence to pharmacological treatment and reducing self-medication, for example. Medina-Córdoba et al.[20] studied factors that contributed to or hindered the comprehension of package inserts by patients, indicating that a language suitable to the patient profile as well as ordered and highlighted structure and organization were examples of characteristics of package inserts that contributed for their comprehension, whereas the presence of scientific language, medical terms, and lack of adequate structure hindered this process. The study reinforced the importance of the quality of package inserts treatment comprehension and adherence, also reducing risk behaviors such as self-medication.

According to the Beers criteria, antiulcer drugs and proton pump inhibitors increase the chances of infection by *Clostridium difficile*, bone loss, and fractures when used for more than eight weeks; these may be used by older adults only in case of a high risk of gastrointestinal lesions.[7] Despite this risk, this information was not found in the package inserts of omeprazole and pantoprazole. The inclusion of these data is important to the rational use of these drugs, especially when long-term use is required.

TABLE 3. Comparison of information on the use of antiulcer drugs, antidiabetic drugs, and NSAIDs by older adults present in professional package inserts and the 2019 Beers criteria.

PIM	Beers 2019	Medication package insert	Comparative analysis	Complementation of package insert
Antiulcer drugs				
Omeprazole	Avoid use for longer than eight weeks. Higher risk of infection by *Clostridium difficile*, bone loss, and fractures	Closer monitoring in older adults	Absent data	Avoid use for longer than eight weeks. Higher risk of infection by *Clostridium difficile,* bone loss, and fractures
Pantoprazole		Daily doses above 40 mg only when treating *H. pylory* infections for up to one week		
Antidiabetic drugs				
Glibenclamide Chlorpropamide	Avoid long-term use in older adults. High risk of severe and prolonged hypoglycemia	Reduced doses. Older adults are more susceptible hypoglycemia	Incomplete data	High risk of severe and prolonged hypoglycemia in older adults
Glimepiride		Similar pharmacokinetics among young and older adults above 65 years old	Discrepant data	
NSAIDs				
Diclofenac sodium Diclofenac potassium Ketoprofen Mefenamic acid Piroxicam	Avoid chronic use in older adults due to high risk of gastrointestinal bleeding and peptic ulcer, in addition to increased arterial pressure and kidney injury	Bleeding, perforations, and ulcers can be more severe in older adults. Kidney function should be monitored. Treatment at the minimum effective dose Higher risk of bleeding and gastrointestinal ulcers. Higher risk of kidney injury and acute renal failure	Incomplete data	Avoid long-term use in older adults, also due to a risk of increasing arterial pressure
Ibuprofen		Caution in patients above 70 years old	Absent data	Avoid chronic use. High risk of peptic ulcer, increased arterial pressure, and kidney injury
Naproxen Ketorolac		Higher risk of bleeding and ulcers in older adults. Use the minimum effective dose	Incomplete data	Avoid long-term use. Higher risk of increased arterial pressure and kidney injury

PIM: potentially inappropriate medication; NSAIDs: nonsteroidal anti-inflammatory drugs; *H. pylori*: Helicobacter pylori.

An important aspect identified in this study is that one-third of the analyzed prescribing information did not present information characterizing the medication as a PIM according to the Beers criteria.[7] The general population considers the package insert as a reliable source of information and often does not research other data; it is thus vital that all clinically relevant considerations be presented in medication package inserts, especially considering the relationship between admissions of older adults to hospital emergency sectors with adverse effects due to the use of PIMs.[22]

The standards and requirements for elaborating package inserts in different countries are considerably heterogeneous. Ramírez-Telles and Argotti-Rodríguez[23] evaluated 25 Latin American and Caribbean countries and observed that only Brazil, Argentina, Chile, Peru, and Venezuela required a clear and defined structure for medication package inserts. Out of the evaluated countries, 32.00% required patient and professional package inserts (including Brazil), 8.00% only required patient package inserts, and 60.00% only required professional package inserts. The study concluded that countries in this region present little consistency in the requirements of their respective regulatory agencies about the content of package inserts, and a standardization of these documents is lacking. The study does not approach aspects referring to the content of package inserts in special populations such as older adults.

Package inserts with accurate and updated information are important to drug safety and efficacy,[15] and this whole process is a responsibility of regulatory agencies. In Brazil, Collegiate Board Resolution (Resolução da Diretoria Colegiada [RDC]) No. 47, published by ANVISA in 2009, provides standards for creating and updating patient and professional package inserts. Documents dedicated to health professionals should present information on contraindications in special populations such as older adults, as well as warnings and precautions directed at these groups; these data are also required in patient package inserts. Both patient and professional package inserts should be made available at the ANVISA electronic record. This resolution also grants the agency the right to demand changes to package inserts whenever new pharmacovigilance data are available or due to technical and scientific reasons.[24]

In the USA, the FDA also establishes rules and guidelines for elaborating package inserts and defines as drug labeling any information provided with the prescription of a drug regulated by the agency. Their main goal is to ensure patient safety, providing health professionals with a summary of the drug's safety and efficacy. The development of prescribing information is not directed at the patients, as a drug's administration is always overseen by a health professional licensed to prescribe it. The package inserts, in addition to containing various topics such as indications, contraindications, precautions, adverse reactions, and interactions, is also required to provide information on the use in specific populations, such as older adults.[25]

In Europe, the European Medicines Agency (EMA) provides information on pharmaceutical products in official approved documents for patients and for health professionals, such as package inserts and the summary of product characteristics (SmPC), and frequently revises their content and conducts research and surveys aiming to update and improve regulatory standards. Regarding the use of medications by older adults, the EMA has the important role of ensuring that their needs are considered throughout drug development, approval, and use in the European Union. For this, the agency designs guidelines and guides (Geriatrics Medicine Strategy [GMS]) which guidance, precautions, and warnings referring to the use of medications by older adults.[26]

Our results are in agreement with other studies and suggest that most package inserts of medications used in Brazil are unsatisfactory and lack important data, enabling inappropriate use of medications and increasing risks of adverse events and hospitalizations, especially among older adults. This is the fastest growing population in Brazil and worldwide, also consuming more medications than any other age group.

In this study, we did not evaluate parameters such as the legibility and comprehension of package inserts, nor did we analyze the proportion of individuals who were used to reading package inserts and whether this habit could affect pharmacotherapy. Future studies are required to analyze the real impact of package insert quality in the rational use of medications and treatment adherence by patients.

CONCLUSION

In this study, none of the analyzed package inserts presented complete information on the risks of PIMs for older adults. Package inserts presented incomplete data or lacked information characterizing the drug as a PIM for older adults. Moreover, even when relevant data were present, we observed a lack of organization when presenting them in some package inserts; no specific sections described the use of the drug by the geriatric population, thus hindering data visualization by professionals and patients.

Our data indicate that some package inserts of drugs used in Brazil are not satisfactory and could lead to higher rates of inappropriate prescribing for older adults along with higher iatrogenesis. It is worth noting the importance of pharmaceutical companies complying with the required technical information and better organizing the content of package inserts, in addition to a more strict surveillance

by ANVISA. Possible strategies for minimizing the use of PIMs by older adults consist in educational measures that favor deprescribing; constant revisions of package inserts of currently used medication; and wide promotion of the Beers criteria along with periodical updates of the Brazilian Consensus on Potentially Inappropriate Medications for Older Adults.

Conflicts of Interests

The authors declared no conflicts of interests.

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Author Contributions

VAAF: formal analysis, data curation, writing – first draft, investigation, methodology, visualization. SLP: project administration, formal analysis, conceptualization, writing – review & editing, investigation, methodology, supervision, validation, visualization.

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