CARDIOVASCULAR DRUG LABELING: DO THEY HAVE INFORMATION ON NECESSARY PRECAUTIONS FOR OLDER PEOPLE?

Bulas de medicamentos cardiovasculares: elas têm informações sobre precauções necessárias aos idosos?

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ABSTRACT

OBJECTIVE: To analyze the existence of information on drug labeling intended for health professionals on the precaution of cardiovascular drugs use in older people. **METHODS:** This is a documentary study, carried out with the analysis of data contained in drug labelings. The existence of information on precautions in the use of drugs for older people as described in the 2016 Brazilian Consensus on Potentially Inappropriate Drugs for Older People (*Consenso Brasileiro de Medicamentos Potencialmente Inapropriados para Idosos de 2016*). **RESULTS:** Of the 29 drugs belonging to the cardiovascular system group that should be avoided by older people and are available in Brazil, 15 are independent of the clinical condition. Of these fifteen, only three drugs (20%) have explicit information in accordance with the Consensus (methyldopa, digoxin, and spironolactone); two (13.33%) have missing explicit information; four (26.66%) have explicitly discordant information; and six drug labels (40%) were categorized as non-explicit information. Regarding drug precautions according to clinical condition, 14 drugs were included. Of these, 12 (85.71%) have equal contraindications of that of Consensus on their drug labels, however, non-explicit; and two (14.28%) contraindications are missing. **CONCLUSION:** Most drug labels lack information on the precautions for the use of drugs in older people. **KEYWORDS:** older people; potentially inappropriate drug list; drug prescriptions; drug labeling.

RESUMO

OBJETIVO: Analisar a existência de informações, em bulas destinadas aos profissionais de saúde, sobre precaução de uso de medicamentos cardiovasculares em idosos. **METODOLOGIA:** Trata-se de estudo documental realizado por meio de análise de dados contidos em bulas de medicamentos. Analisou-se a existência, na bula, de informações sobre precauções no uso de medicamentos para idosos, conforme descrito no Consenso Brasileiro de Medicamentos Potencialmente Inapropriados para Idosos de 2016. **RESULTADOS:** Dos 29 medicamentos pertencentes ao grupo do sistema cardiovascular que devem ser evitados por idosos e estão disponíveis no Brasil, 15 independem da condição clínica prévia do paciente para que sejam vetados para os idosos. Desses 15, apenas 3 medicamentos (20%) têm informações explícitas concordantes com o Consenso (metildopa, digoxina e espironolactona); 2 (13,33%) têm informações explícitas ausentes; 4 (26,66%) têm informações explícitas discordantes; e 6 bulas (40%) foram categorizadas como informações não explícitas. Quanto às precauções dos medicamentos de acordo com a condição clínica do paciente, incluíram-se 14 medicamentos que devem ser evitados por idosos e estão disponíveis no Brasil. Destes, 12 (85,71%) têm em suas bulas recomendações concordantes com o Consenso, porém não explícitas, e 2 (14,28%) não têm as contraindicações. **CONCLUSÕES:** A maioria das bulas carece de informações sobre precauções de uso de medicamentos para a população idosa. **PALAVRAS-CHAVE:** idosos; medicamentos potencialmente inapropriados; prescrições medicamentosas; bula de medicamentos.

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INTRODUCTION

The demographic growth of the older population in recent years is evident, a fact explained by the improvement in living conditions, and also by scientific and technological improvement.¹ At the same time, there is the growing phenomenon of multimorbidity, which leads this population to great demand for health services and a high drug consumption.² Literature shows that the rate of drug use by older people is approximately 80%, thus representing the main consumers of these therapeutic inputs worldwide.³ In agreement with these facts, information from the National Survey on Access, Use and Promotion of Rational Use of Medicines in Brazil (*Pesquisa Nacional sobre Acesso, Utilização e Promoção do Uso Racional de Medicamentos no Brasil* - PNAUM) shows that 93% of older Brazilians chronically use at least one drug, and 18% use polypharmacy.⁴

Also important is the fact that older people have physiological changes related to age, such as reduced liver and kidney functions, and changes in body composition, which affect the pharmacokinetics and pharmacodynamics of drugs.⁵ Therefore, there was a need to create lists of explicit criteria for use precaution of potentially inappropriate drugs (PIM), in order to mitigate the risks of prescribing these drugs, such as the 2019 Beers Criteria⁶ and the Brazilian Consensus on Potentially Inappropriate Medicines for Older People (*Consenso Brasileiro de Medicamentos Potencialmente Inapropriados para Idosos* - CBMPPII), which contribute with the quality and safety of prescriptions for this population.⁷

The use of PIM by older people is a research topic in Brazil and in the world because the promotion of health and care to this population proves to be increasingly needed.⁸ Thus, the rational drug use by older people is of fundamental importance to avoid adverse events that may harm the health and quality of life of this population, who is growing at a rapid pace.^{5,8}

In the context of PIM use, Brazilian studies show that drugs that act on the cardiovascular system are involved in 40 to 56% of all medical prescriptions for older people.^{9,10} Given this, critically analyzing the precautions contained in drug labels is essential to generate evidence on the need for possible changes in regulatory agencies, pharmaceutical industries, and clinical practice.

The objective is to analyze the existence of information on precaution for the use of cardiovascular drugs in older people contained on drug labels for health professionals.

METHODS

The present paper consists of a documentary study, in which data contained in the electronic drug labels made

available by the Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária* - ANVISA), on the website: http://www.anvisa.gov.br/datavisa/fila_bula/index.

Information from the CBMPPII was the reference used as a standard of comparison with the information on the drug label. The analysis considered drugs that should be avoided independently or depending on the older person's previous clinical condition. In CBMPPII, there is information warning about the use of these drugs in this population. Information is based on effectiveness, adversities, and precautions and/or contraindications.⁷

Drugs related to the cardiovascular system, present in the CBMPPII, were identified, and their availability in Brazil was reviewed and consulted on the ANVISA website (<https://consultas.anvisa.gov.br/#/medicamentos/>). Thereby, drug labels whose registration status was "expired/canceled" were not included in analysis.

Drugs were divided into two groups: those that contain precautions regardless of the person's clinical condition and those that depend on the person's clinical condition. Then, the respective instructions for professionals were sought. If more than one drug labeling and/or drug labels from different laboratories were found, the most recent publication was considered.

After selecting the drug labels for cardiovascular system medications available in Brazil that are independent of the person's clinical condition, the presence or absence of explicit information on precautions for use for older people was first identified, considering an individual aged 65 years or older as an older person. After identifying information, it was categorized into: "explicit information" and "non-explicit information". "Explicit" were those in which the drug labeling provided information on precautions, in the title and/or in the body of the text, containing the descriptors "older people", "special population", and/or "65 years old". "Non-explicit" information was when drug labels did not have this specification.

Then, explicit information on drug labels was compared to the descriptions contained in CBMPPII,⁷ and whether such information was concordant, discrepant, or missing was analyzed.

Concordant information was considered when drug labels contained information similar to the justification provided by the CBMPPII when determining that the drug should be avoided in older adults; discrepant, if the information on drug labels was opposed to the CBMPPII; and missing information, if the reason described by the CBMPPII was not mentioned on the drug label. It was considered as "non-explicit information" when the drug

label did not have a specific section for the population studied, regardless of whether its content agreed, discordant, or missing from the CBMPPII. Thus, after the critical comparison between the information contained in drug labels and that of the CBMPPII, information was categorized into:

- concordant explicit information;
- conflicting explicit information;
- missing explicit information;
- non-explicit information.

The synthesis of the data collection process is described in Figure 1.

As for the drugs that should be avoided in older people according to their clinical condition, it was analyzed, first, whether the justification for avoiding the use mentioned by CBMPPII was present in drug labels. If so, whether such information was specified for the older population or not as then observed. Thus, information was categorized as “explicit”, “non-explicit”, and “missing”.

For comparing information on the precautions for older people available on drug labels and in the CBMPPII,⁷ documentary analysis of each drug labeling was carried out by two researchers independently. To analyze and interpret the data, a database in the form of spreadsheets was built using Microsoft Office Excel 2016.

Figure 1 Flowchart of the data collection process.

RESULTS

Of the 23 drugs belonging to the cardiovascular system group that should be avoided by older people, regardless of the person's clinical situation, listed by CBMPPII, eight of them have no active registration with ANVISA. Therefore, 15 drug labels for professionals were analyzed (Chart 1). There are duplicate drugs, but they were analyzed separately, given that the context in which they are inserted in the CBMPPII is different.⁷

Information contained in 40% of drug labels (n = 6) was categorized as non-explicit information, 13.33% (n = 2) as

missing explicit information, 26.66% (n = 4) as conflicting explicit information, and 20% (n = 3) as concordant explicit information.

As for the drugs listed by the CBMPPII that should be avoided in certain clinical conditions and that act on the cardiovascular system, 14 were selected, because of the 18 drugs listed by the CBMPPII, one is not marketed in Brazil, and three have no active registration for use as vasodilators.

Considering that there are duplicate drugs, 85.71% of information on drug labels (n = 12) were categorized as non-explicit, and 14.28% (n = 2) as missing (Chart 2).

Chart 1 Comparison between the contents of the drug label and the description of the precautions for use contained in the Brazilian Consensus on Potentially Inappropriate Medicines for Older People for cardiovascular drugs.

Drugs contained in the CBMPPII	Justification according to the CBMPPII	Content of the explicit information	Comparative analysis between information on the drug label and that of the CBMPPII
Doxazosin	Use associated to a high risk of orthostatic hypotension. Not recommended for routine treatment of hypertension. There are alternatives with better risk-benefit ratio	It states that there are no specific recommendations for older people	Missing explicit information
Clonidine	High risk of adverse effects to the Central Nervous System (CNS). It may cause bradycardia and orthostatic hypotension	In the section on adversities and precautions, it does not quote the descriptors to be considered explicit information	Non-explicit information
Methyldopa		Occurrence of syncope	Concordant explicit information
Amiodarone	Data suggest that heart rate control provides a better risk-benefit profile than rhythm control in older people. Amiodarone is associated to thyroid disease, lung disorders and prolongation of the QT interval	More pronounced reduction in heart rate	Missing explicit information
Propafenone		No differences were observed in the safety or efficacy of the drug when used by older people	Conflicting explicit information
Sotalol		Beta-adrenergic blocking agents have been used safely and effectively in older people	Conflicting explicit information
Acetylsalicylic acid dose > 150 mg/day	Increased risk of gastrointestinal bleeding, with no evidence of increased efficacy	In the side effects and precautions section, it does not quote the descriptors to be considered explicit information	Non-explicit information
Acetylsalicylic acid to treat dizziness not clearly attributable to cerebrovascular disease.	Increased risk of gastrointestinal bleeding, with no evidence of increased efficacy	In the side effects and precautions section, it does not quote the descriptors to be considered explicit information	Non-explicit information

CBMPPII: Brazilian Consensus on Potentially Inappropriate Medicines for Older People (*Consenso Brasileiro de Medicamentos Potencialmente Inapropriados para Idosos*).

Chart 2 Comparison between drug labels for drugs that act on the cardiovascular system and the description of precautions for use contained in the Brazilian Consensus on Potentially Inappropriate Medicines for Older People (CBMPPII) dependent on clinical condition.

Drugs contained in the CBMPPII	Justification according to the CBMPPII	Comparative analysis between information on the drug labeling and that of the CBMPPII
Acetylsalicylic acid	High risk of bleeding in patients with concomitant hemorrhagic disorder	Non-explicit contraindication
Clopidogrel		Non-explicit contraindication
Dipyridamole		Missing contraindication
Warfarin		Non-explicit contraindication
Diltiazem	Possible worsening of constipation	Non-explicit contraindication
Verapamil		Non-explicit contraindication
Carvedilol	Increased risk of bronchospasm	Non-explicit contraindication
Propranolol		Non-explicit contraindication
Hydrochlorothiazide	Possibility of aggravating gout	Non-explicit contraindication
Chlortalidone		Non-explicit contraindication
Diltiazem	Potential to promote fluid retention and aggravation	Non-explicit contraindication
Verapamil		Non-explicit contraindication
Cilostazol	Potential to promote fluid retention and exacerbate heart failure	Non-explicit contraindication
Hydralazine	Risk of syncope, falls	Missing contraindication

DISCUSSION

When analyzing information on drug labels and CBMPPII critically, there are significant gaps in the contents of the Brazilian drug labels with regard to the precautions for use in older people, given only three of the cardiovascular system medications have concordant explicit information.

Four drugs — propafenone, sotalol, and furosemide (the latter being presented twice by the CBMPPII) — have explicit information that differs from that of CBMPPII. Interestingly, the content of such information concerns drug effectiveness, considering that the CBMPPII warns about the existence of better options on the market in terms of results of using these drugs.⁷ Observing this conflict, ANVISA should encourage the publication of clinical results of drugs efficacy so that, even if there are differences between studies and drug labels, the prescribers, in case of doubt or lack of better options in the environment in which the person is inserted, have greater scientific basis for decision making. This already occurs at the European Medicines Agency, which obliges manufacturers to make the protocols and results of safety studies public.¹¹

Two drugs (amiodarone and doxazosin) have missing explicit information, once the justification reported by the

CBMPPII was not found in the selected sections of these drug labels. Amiodarone is considered at risk, according to the CBMPPII, because it is associated to thyroid disease, lung disorders, and prolongation of the QT interval. This is one of the main drugs associated to adverse events. When the clinical condition of older people requires its use and it cannot be replaced, strict monitoring of the cardiovascular system and possible adverse effects should be performed.^{7,12}

Finally, six drug labels analyzed do not have any specific precautions for older people. The drugs in these drug labels are clonidine, dipyridamole, ticlopidine, nifedipine, and acetylsalicylic acid (this is found in two different contexts in the CBMPPII). Acetylsalicylic acid increases the risk of severe bleeding, especially intestinal bleeding in older people.^{7,13} Besides that, the daily use of this drug tends to be higher in older people due to the higher incidence and greater risk of heart disease in this age group.^{14,15} Therefore, their prescription should be made with caution and consider its risks and benefits.

When paying attention to the fact that drugs that act on the cardiovascular system are potential risk factors for adverse events, the results of this study are worrying, given that older

people use these drugs with high frequency. The adverse impact on quality of life and costs are also significant, because they increase the chances of health problems, such as admissions to emergencies, hospitalizations, or even death.^{12,16} In addition, the minority of drug labels of the studied drugs have explicit content for older people and are in accordance with the clinical warnings provided by the CBMPPII.⁷

Drug labels aim to make information clear in order to contribute to the rational and safe use of drugs.¹⁷ Despite technical limitations, drug labels are ways of disseminating and consulting information for both professionals and users.^{18,19} Therefore, it is of utmost importance that drug labels are written in a complete manner, so that the prescribing physician, the clinical pharmacist, the user and even the pharmaceutical industry have quality information, updated and in line with the epidemiological profile of Brazil.¹⁷

In this context, ANVISA published a Collegiate Board Resolution (*Resolução de Diretoria Colegiada - RDC*) No. 47 of 2009 to standardize and assist in the preparation of quality information on drug labels in Brazil. This resolution recommends that all drugs must have specific instructions for users and professionals, which must be contained in the Electronic Drug Labels of ANVISA. Such drug labels must contain contraindications, warnings, and precautions, when applicable, for special populations — for example, older people.²⁰

All the drug labels analyzed have a publication date later than 2016, that is, after the publication of the CBMPPII and RDC No. 47 of 2009.^{7,20} However, the present study demonstrated that, even with the existence of standardization standards that aim at improving information on drugs and with the publication of the CBMPPII,⁷ drug labels that work on the cardiovascular system studied lack technical and legal information. This is something undesirable, since, in addition to drug labels being based on evidence, they must also be updated according to clinical information.²¹ Moreover, information contained on drug labels can influence clinical decision-making and, thus, compromise the quality of care based on clinical evidence.²²

Thus, adequacy on the part of the pharmaceutical industries in the production of drug labels, and greater rigor in the approval and inspection carried out by ANVISA should take place. In addition, given the growing life expectancy and the fact that older people are considered a special population, a specific and explicit section on drug labels for older people would be mandatory, regardless of whether or not there are differences between this population and the others.

Although the present study is limited to the analysis of cardiovascular system drugs, it highlights the need to adapt drug labels to technical and legal information that contribute

to the care process of older people, which is the fastest growing population in Brazil and worldwide, besides being the age group that uses the most drugs.

CONCLUSION

The study showed that only a small portion of drug labels that act on the cardiovascular system have explicit information in accordance with that contained in the CBMPPII when it comes to older people. The lack of information and the existence of technical content that does not corroborate the scientific literature can cause serious consequences, such as increased errors in the prescription of drugs and risk of adverse events.

Therefore, explaining the possible adverse events and precautions regarding the use of drugs by older people on drug labels for professionals and users is essential, in order to contribute to the rational use and reduce the risks of use by this population.

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CONFLICT OF INTERESTS

The authors declare there is no conflict of interests.

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AUTHORS' CONTRIBUTION

LOM: conceptualization, data curation, formal analysis, writing — original draft or review & editing. RCV: conceptualization, data curation, formal analysis, writing — original draft or review & editing. AOB: conceptualization, data curation, formal analysis, writing — original draft or review & editing. ACNRP: writing — original draft or review & editing. FMDC: conceptualization, data curation, formal analysis, writing — original draft or review & editing.

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