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POTENTIALLY INAPPROPRIATE MEDICATIONS FOR THE ELDERLY IN THE UNIFIED HEALTH SYSTEM AND THEIR THERAPEUTIC ALTERNATIVES

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Abstract: **Objective:** To identify and propose substitutes for potentially inappropriate medications (PIMs) for elderly people present in the essential medication lists of the Unified Health System: REMUME-SP 2016, RENAME 2020 and 2022. **Methodology:** Descriptive study, which compared these lists with the latest versions of the STOPP (2015) and Beers (2019) criteria to indicate PIMs, and suggested therapeutic alternatives based on literature data. **Results:** In RENAME 2020, 105 MPIs were found, while in RENAME 2022, 106 MPIs, representing 21% of the list of drugs on these lists. In REMUME-SP, 120 MPIs were identified, being 27% of its items. Regarding therapeutic alternatives, the lists showed from 47% to 65% of PIMs with other options present in these same lists. Although they have differences, the three documents showed 80 MPIs in common, with a predominance of those that act on the central nervous and cardiovascular systems. **Conclusion:** It is important to prioritize safer therapeutic options for the elderly among the essential medicines available in the country, or when it is not possible, to follow the recommended actions, such as dose reduction or the adoption of a non-pharmacological treatment. Funding: This research was funded by the São Paulo Research Foundation (FAPESP) – process nº 2021/01474-2. such as the dose reduction or the adoption of a non-pharmacological treatment. **Funding:** This research was funded by the São Paulo Research Foundation (FAPESP) – process nº 2021/01474-2.

Keywords: List of Potentially Inappropriate Medications; Access to Essential Medicines and Health Technologies; Elderly.

INTRODUCTION

Worldwide, the phenomenon of Demographic Transition is recurrent, characterized by a reduction in birth and death rates, leading to an increase in life expectancy and, therefore, the aging of the population.[1]

Associated with it, there is the Epidemiological Transition, with a paradigm shift: from a young country, with the presence of infectious and contagious diseases, to a more mature country, marked by chronic non-communicable diseases (NCDs) associated with the elderly population.[2] Thus, the NCDs require continuous pharmacological treatment with an increasingly high number of drugs, bringing an increased risk of adverse events.[3]

In this scenario, there are potentially inappropriate medications (PIMs) for the elderly, defined as those that offer more risks than benefits to this population and for which there are safer therapeutic alternatives.[4]

The use of PIMs among the elderly is a serious public health problem, as it is intrinsically linked to increased comorbidity and mortality, causing high costs for the public health system.[5]

At this juncture, Mark Beers and collaborators,[4] using the Delphi method, developed a consensus containing 30 items that would be inappropriate for elderly people in a long-term care facility in California, United States.

In the European context, in order to solve some deficiencies in Beers, such as the fact that many drugs indicated by this instrument were not marketed in the continent in question, criteria were developed STOPP (Screening tool of older people's prescriptions), which were updated in 2015, resulting in its latest version.[6]

In Brazil, through its public health system, called the Unified Health System (SUS), medicines are available on national, state and municipal lists. Essential medicines have proven efficacy and safety, with a better cost-benefit ratio and are selected to serve the population as a whole. However, some may be

considered inappropriate for the elderly.[7]

In 2019, the national list was updated, establishing the National List of Essential Medicines (RENAME) 2020,[8] and more recently, in 2022, its last version was instituted, being RENAME 2022.[9] As for the city of São Paulo, it is found the Municipal List of Essential Medicines (REMUME-SP), and in 2016, its 3rd edition[10] was published.

In this scenario,based on a literature review carried out by the researcher, no studies were found that evaluated PIMs in the latest versions of the national list, RENAME 2020[8] and 2022,[9] nor the municipal list of São Paulo, REMUME-SP 2016.[10]

Added to this, considering that there have been updates to the identification instruments themselves in recent years, namely the STOPP criteria in 2015[6] and Beers in 2019,[11] it is even more necessary to use these new lists in the search for PIMs among the list of drugs essential drugs in the country and the search for substitute medicines, which are present in the mentioned list of medicines and which do not pose risks to the elderly population.

Thus, the present study aimed to identify and propose substitutes for potentially inappropriate medicines for the elderly present in the list of essential medicines of the Unified Health System: RENAME 2020, RENAME 2022 and REMUME-SP 2016.

METHODOLOGY

TYPE OF STUDY, STUDIED POPULATION AND VARIABLE OF INTEREST

This is a descriptive study that identified the PIMs for the elderly present in the last versions of two lists of essential medicines of the SUS: RENAME of 2020; and REMUME-SP, 2016; and proposed therapeutic alternatives present in the same lists, through literature data. In addition, the 2022 version of RENAME was also analyzed, both in identifying PIMs and in proposing other safer options.

The studied population consisted of the universe of drugs available in the last version of REMUME-SP[10] and RENAME of 2020.[8] In 2022, with the publication of the RENAME edition of that year,[9] its list of drugs was also included.

The variable of interest was the number of potentially inappropriate medications for the elderly (PIMs), being a dichotomous variable, dependent on the quantification of medications present in the RENAME and REMUME-SP editions used, which have been indicated as inappropriate by the 2015 STOPP instruments,[6] and Beers of 2019.[11]

These instruments for identifying PIMs were chosen because, while Beers is located in a North American context, STOPP is in a European scenario, and, therefore, it is expected to find differences regarding the indications of inappropriate medication for the elderly. Thus, using both criteria, the aim is to obtain a greater ability to recognize PIMs in the Brazilian reality.

DATA COLLECTION AND ANALYSIS TO IDENTIFY MPIS

Document analysis was used for data collection, and consisted of 3 steps: 1) translation and transcription of the STOPP6 and Beers criteria;[11] 2) checking of items considered inappropriate by these instruments in REMUME-SP 2016[10] and RENAME 2020;[8] 3) setting up a database containing these items in an Excel® spreadsheet. Subsequently, with the publication in 2022 of the RENAME of that year,[9] its lists of inclusions and exclusions were analyzed, through which the constant PIMs were identified.

The first stage was based on the use of the most recent versions of Beers, from 2019,[11] and STOPP, from 2015.[6] They were obtained in searches of reference bases carried out in January 2021. At the beginning of data

collection, in July 2021, no new versions of said documents were found. For each instrument, the items were translated and transcribed into two different Excel® spreadsheets.

Once the potentially inappropriate medications and drug interactions for the elderly were identified by the identification instruments used, these medications were checked against the RENAME and REMUME-SP lists. Those found were transcribed into another database in Excel®.

Considering that a pharmacological class is often identified as inappropriate, the Anatomical Therapeutic Chemical Classification (ATC)[12] was used to determine the drugs that compose it, and which of them are included in the lists of essential drugs addressed.

PROPOSAL OF THERAPEUTIC ALTERNATIVES

Obtaining the PIMs present in the lists of essential medicines addressed, therapeutic alternatives were suggested based on the mechanisms of action, safety of using medicines for the elderly and therapeutic classes, prioritizing existing medicines in the standardized lists themselves. For this, the options presented by articles from bibliographical research in the PubMed database were listed.

This bibliographical research was carried out in October 2021, and included the period from 05/14/2015 to 09/01/2021. The following health descriptors were used:"alternative" AND "potentially inappropriate medication list (MeSH Terms)". In addition, other publications of interest were selected through a manual consultation based on the references of the articles found in PubMed, paying attention to the titles and abstracts that were related to the theme.

Articles containing options for the MPIs found in the RENAME and REMUME-SP editions, written in English, Spanish and French, were included. This selection was made by one reviewer.

Having the therapeutic alternatives proposed by the aforementioned means, two new spreadsheets in Excel® were prepared, one for each list of essential medicines, containing the suggested substitutes. In them, the PIMs found were divided according to the ATC Classification,[12] pharmacological class, reason for inadequacy according to Beers and STOPP and which of the instruments indicates it, and the proposed alternatives.

In the same way carried out in the collection of PIMs, considering the publication of RENAME 2022, the items present in the inclusion and exclusion lists contained in this list of medicines were analyzed, from which it was possible to identify the possible therapeutic substitutes that were added or excluded regarding RENAME 2020.

STATISTICAL ANALYSIS

Descriptive statistical analysis (absolute numbers and percentages) was performed for the MPIs of REMUME-SP 2016, RENAME 2020 and RENAME 2022, based on pharmacological and ATC groups,[12] respectively. The same occurred with regard to therapeutic alternatives for PIMs on the national lists and those in the city of São Paulo.

ETHICAL ASPECTS OF RESEARCH

Because it is a research that involves analysis of published documents and open access, the evaluation of the Research Committee of the research executing unit was waived, in accordance with Resolution 466/12 of the National Health Council.

FINANCING

This research was financed by the State of São Paulo Research Foundation (FAPESP) - process nº 2021/01474-2.

RESULTS

In RENAME 2020, 105 MPIs were identified, while in REMUME-SP 2016, 120 MPIs were found. These are inappropriate medications per se (whether for the elderly in general, for those with certain conditions, medications that must be used with caution or that must be adjusted in dosage according to renal function) and medications present in drug interactions potentials.

In RENAME 2022, 106 MPIs were observed, with the addition of 3 MPIs (sacubitril valsartan sodium hydrated, tiotropium bromide monohydrate + olodaterol hydrochloride and umeclidinium bromide + vilanterol trifenatate) and the exclusion of 2 MPIs (aluminum hydroxide and ranitidine hydrochloride) in relation to RENAME 2020.

In all, excluding repetitions, 142 MPIs were identified (considering REMUME-SP + RENAME 2020) and 145 MPIs (for REMUME-SP + RENAME 2022), which can be seen in **Table 1**.

According to the count carried out by the researchers, in RENAME 2020, considering the total of 500 items, 21% (105) of them are MPIs. In the REMUME-SP 2016, which has a total of 443 items, 27% (120) of the medications are classified as potentially inappropriate. Finally, in RENAME 2022, with a total of 516 items, 21% (106) are MPIs.

Dividing the PIMs found according to the ATC Classification,[12] **Table 2** was obtained. In these relationships, there is a prevalence of PIMs that act on the nervous system, followed by those that act on the cardiovascular and digestive systems.

POTENTIAL DRUG INTERACTIONS

According to Beers[11] and/or STOPP,[6] 74 drugs participating in potential drug interactions were found in RENAME 2020, 75 in RENAME 2022 and 85 in REMUME-SP 2016, see **Table 3**.

MEDICATIONS THAT MUST BE USED WITH CAUTION

Table 4 shows the drugs that require careful use, informed only by the Beers instrument.[11] In this case, there are no therapeutic options, but rather, the aim is to use them with caution. Both in RENAME 2020 and RENAME 2022, 19 items were found, while in REMUME-SP 2016, 24 drugs fit the use with care.

DRUGS THAT MUST PAY ATTENTION TO KIDNEY FUNCTION

The drugs that need attention regarding the renal function of the elderly are presented in **Table 5**. Similar to the drugs that must be used with care, there are no proposals for therapeutic alternatives, and the recommendation for these items is the interruption of use or reduction of dose, according to Beers[11] and/or STOPP.[6] In RENAME 2020 and RENAME 2022, 14 items were found, and in REMUME-SP, 17.

THERAPEUTIC ALTERNATIVES

The bibliographic search on PubMed, carried out in October 2021, resulted in 25 articles. One in Chinese and 16 that did not offer therapeutic alternatives were excluded. In addition, seven more articles were obtained by manually consulting the references of the articles found in the previously described bibliographic search. Thus, in all, 15 publications were used.

Only PIMs were considered eligible for possible replacements for most elderly people and for those with certain conditions, since the drugs indicated as "use with care" and "pay attention to kidney function" have other solutions, not being the proposal of alternatives, but the use with caution, interruption or reduction of the dose.

In this scenario, in relation to RENAME

2020, 94 MPIs were eligible to receive alternatives – increasing to 95 MPIs in RENAME 2022 – and in terms of REMUME-SP, 109. Of these, in terms of RENAME 2020 and 2022, respectively, 47% (44/94 and 45/95) of the PIMs presented other therapeutic options, 29% (27/94) and 28% (27/95) recommended measures such as dose reduction or adoption of non-pharmacological treatment and 24% (23/94 and 23/95) had no alternatives. Regarding the REMUME-SP, 60% (65/109) of the MPI presented alternatives, 25% (27/109) suggested other interventions and 15% (17/109) did not have substitutes.

Particularly for REMUME-SP, the following combinations were disregarded as likely to receive therapeutic alternatives: sodium dipyrone + promethazine + adiphenine, scopolamine + sodium dipyrone and spironolactone + hydrochlorothiazide. This is because its separate components are already inappropriate for the elderly, having their own substitutes, which were considered in the database.

DISCUSSION

In this research, it was found that 21% (105/500) of RENAME 2020, 21% (106/516) of RENAME 2022 and 27% (120/443) of REMUME-SP 2016 are PIMs for the elderly. These standardized drug lists have 80 PIMs in common, representing 76% of PIMs in RENAME 2020, 75% in RENAME 2022 and 67% in REMUME-SP. As for their differences, RENAME 2020 features 23 unique MPIs, the 2022 edition, 26 MPIs, and while REMUME-SP, 38 unique MPIs.

Compared to previous publications that sought PIMs, in RENAME 2010, the number of PIMs present ranged from 20[13] to 31.[14] Later, in RENAME 2012, there were 31.[13] and in RENAME 2013, 35 PIMs.[15] Thus, a considerable increase was observed in the number of these drugs with that found in this work, which was 105 PIMs in RENAME 2020 and 106 in RENAME 2022. Between the last two versions of the document, no significant changes were seen, showing 103 PIMs in common.

Furthermore, this comparison cannot be made in the case of REMUME-SP, whose 2016 version has 120 MPIs according to the findings of this work. This is because no articles were found in the literature that quantified the PIMs present in this list of essential medicines.

In this scenario, several works in the literature proposed not only to list medications that could bring risks to the elderly population, but also to propose therapeutic options for them, a task not performed by the instruments of Beers[11] and STOPP.[6]

However, these publications were not able to provide alternatives for all drugs indicated as inappropriate. Therefore, based on the mechanisms of action and pharmacological classes, possible substitutes for MPIs were proposed: aluminum hydroxide (sodium bicarbonate), mineral oil (glycerol, lactulose or magnesium sulfate in RENAME 2020 and 2022, and glycerol, lactulose or mannitol in REMUME-SP) and ipratropium bromide (fenoterol, formoterol, salbutamol or salmeterol).

On the other hand, many alternatives proposed by these articles in the literature still pose risks for the geriatric population, according to Beers and/or STOPP. For example: as a substitute for ranitidine, omeprazole was suggested,[16],[17] although this was also indicated as inappropriate according to the aforementioned instruments. In this sense, Clyne et al.[18] recommend reducing the dose or interrupting the treatment using omeprazole.

Added to this, even when an entire class of drugs is identified as potentially harmful, these publications suggest some drug within this group as an option. This could

be seen in the case of non-steroidal anti-inflammatory drugs (NSAIDs), which were marked as inappropriate, but for pain and analgesia, dipyrone[19] and paracetamol were recommended.[17,19,20,21]

Still with regard to NSAIDs, a special case is that of acetylsalicylic acid. This is because, although it is inappropriate as an anti-inflammatory, it is advised as an antithrombotic agent if used in low doses.[16,17,19,20,21,22,23,24,25,26]

Regarding antidepressants, it is possible to observe differences in the list of essential drugs analyzed in terms of the supply of substitutes. Considering tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) to be inappropriate, in RENAME there is only bupropion as another antidepressant option. At REMUME-SP, there is the option of sertraline, which is recommended as the best alternative, even though it is an SSRI.[16,17,19,20,21,22,23,25,26,27,28]

Another relevant class in the context of PIMs that act on the nervous system are the antipsychotics. In general, haloperidol, olanzapine, quetiapine or risperidone are preferred.[16,21,22,23,25,27,28]

In addition, regarding antipsychotics, the STOPP[6] criteria emphasize avoiding their use in elderly people with Parkinson's disease, with the exception of quetiapine and clozapine. In turn, Forgerini et al.[28] report that risperidone and quetiapine are the recommended alternatives when the use of antipsychotics is unavoidable, as they have a shorter half-life when compared to the other drugs of the class.

Moving on to benzodiazepines, priority is given to the use of those with shorter duration when compared to those of long duration.[21,22,23,25,26,28,29] In this sense, in RENAME 2020 and 2022, there is the option of midazolam, while at REMUME-SP, midazolam and lorazepam are stopped.

With regard to antiepileptics, there is a predilection for valproic acid, carbamazepine, gabapentin, lamotrigine or levetiracetam as better alternatives to be used.[16,17,19,25,27]

Moving on to MPIs that act on the cardiovascular system, although beta-adrenergic blockers are inappropriate for STOPP, publications containing replacements recommend changing non-selective blockers, with propranolol and pindolol (the latter appearing only in the list of the municipality of São Paulo), by cardioselective blockers, such as atenolol, carvedilol and metoprolol.[16,21,24]

Similarly, although amlodipine has its inappropriateness indicated by STOPP (due to the fact that it is a calcium channel blocker),[6] it is suggested as a substitute for other drugs of the same class, such as nifedipine.[16,22,23,25,26,29,30]

In the same sense, angiotensin-converting enzyme (ACE) inhibitors, such as captopril and enalapril, are pointed out by STOPP as potentially inappropriate, but on the other hand, they are seen as possible choices compared to other hypertensives.[16,17,21,23,25,26,30] In turn, Kojima et al.[24] advise, when the individual is intolerant to ACE inhibitors, the use of losartan potassium.

Moving on to conjugated estrogens, there is a divergence of recommendations. At the same time that some of these articles propose an association with progesterone,[20,21] the Beers[11] criteria argue that even performing this association, it would still be potentially inappropriate for the elderly.

Nevertheless, this study has some limitations. It was a scientific initiation work, developed using only two instruments for evaluating inappropriate medications for the elderly in two of the numerous lists of essential medicines available in the country. However, these are the two most used instruments, either because of the tradition of use; the reference in territorial context, including important representative societies of the local medical and scientific community: Beers and STOPP criteria.

In addition, another limitation is based on the fact that the literature search for substitutes was performed only on the PubMed primary reference base and by a single reviewer: scientific initiation student. However, using the systematized review criteria.

Finally, it is worth mentioning that, whether in terms of avoiding the use of drugs that could pose risks to the elderly population, or in an attempt to replace these elements with therapeutic alternatives, it is important to take into account the individual assessment of each prescription and patient, which must take into account other aspects such as the purpose of treatment and individual responses.[16] In addition, reducing the use of PIMs is just one of the strategies that can be adopted for a better pharmacotherapy of the elderly, and other measures can be carried out together .[21]

CONCLUSION

As can be seen in this work, there is some divergence between the possible alternatives and disagreement regarding which drugs are considered inappropriate, in addition to the fact that, many times, the proposed substitutes may also be inappropriate.

Despite these limitations, it is important to prioritize therapeutic options, or when this is not possible, to follow the recommended procedures. These points, addressed by this work, aim to help in making clinical decisions, in addition to collaborating with future incorporations in the lists of standardized medicines in the country.

APPENDICES

Available in the free Open Science Framework (OSF) repository:https://osf.io/yjpfz/or DOI 10.17605/OSF.IO/YJPFZ.

ASSIGNMENTS

Bruno Siraama

Roles: Conceptualization, data curation, methodology, funding acquisition, writing – original draft, writing – review and editing.

Eliane Ribeiro

Roles: Conceptualization, methodology, funding acquisition, writing – review and editing.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest, being associated only with ‘’Universidade de São Paulo”.

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MPI	RE_{20}	RE_{22}	REM	MPI	RE_{20}	RE_{22}	REM	MPI	RE_{20}	RE_{22}	REM
Acetylsalicylic acid	X	X	X	Spironolactone	X	X	X	nimodipine			X
abciximab	X	X		Spironolactone + Hydrochlorothiazide			X	Nitrazepam			X
Valproic Acid (Sodium Valproate)	X	X		Conjugated Estrogens	X	X	X	Nitrofurantoin	X	X	X
Sodium alendronate	X	X	X	Ethosuximide	X	X		Nortriptyline	X	X	X
aluminum, hydroxide	X		X	Phenytoin or Sodium Phenytoin	X	X	X	olanzapine	X	X	X
amiodarone	X	X	X	phenobarbital	X	X	X	Mineral oil	X	X	X
Amitriptyline	X	X	X	sodium phenobarbital			X	omeprazole	X	X	X
Amlodipine	X	X	X	Fentanyl			X	omeprazole sodium			X
Atenolol	X	X	X	iron, sulfate	X	X	X	Oxybutynin			X
Atropine	X	X	X	fludrocortisone	X	X		disodium pamidronate	X	X	
Betamethasone,	X	X	X	fluoxetine	X	X	X	paracetamol	X	X	X
Bromazepam			X	Furosemide	X	X	X	Pericyzine			X
Bromocriptine	X	X	X	Gabapentin	X	X	X	pethidine			X
Cabergoline	X	X	X	galantamine	X	X		Pindolol			X
captopril	X	X	X	glibenclamide	X	X	X	pyridostigmine	X	X	
carbamazepine	X	X	X	haloperidol	X	X	X	pramipexole	X	X	
carvedilol	X	X	X	haloperidol, decanoate	X	X	X	Prednisolone	X	X	X
ketoprofen			X	hydrochlorothiazide	X	X	X	prednisone	X	X	X
Ciprofloxacin	X	X	X	hydrocortisone	X	X	X	Primidone	X	X	
clarithromycin	X	X	X	hydroxyzine			X	Promethazine	X	X	X
Clobazam	X	X	X	Ibuprofen	X	X	X	propranolol	X	X	X
Clomipramine	X	X	X	Iloprost	X	X		quetiapine	X	X	X
clonazepam	X	X	X	imipramine			X	Ranitidine	X		X
Clonidine			X	indomethacin			X	Remifentanil			X
Clopidogrel	X	X	X	Fast-acting insulin analogue	X	X		risedronate sodium	X	X	
Chlorpromazine	X	X	X	regular human insulin	X	X	X	Risperidone	X	X	X
Clozapine	X	X	X	Ipratropium	X	X	X	Rivastigmine	X	X	
Codeine	X	X	X	Isosorbide, dinitrate or propathylnitrate	X	X	X	sacubitril valsartan		X	
colchicine			X	Isosorbide, mononitrate	X	X	X	sertraline			X
Desmopressin	X	X	X	Lamotrigine	X	X	X	sildenafil	X	X	X
dexamethasone	X	X	X	Levetiracetam	X	X		sufentanil			X
Dexamethasone, Disodium Phosphate	X	X	X	Levodopa + Benserazide	X	X	X	Sulfamethoxazole + Trimethoprim	X	X	X
Dexchlorpheniramine	X	X	X	Levodopa + Carbidopa	X	X	X	theophylline			X
diazepam	X	X	X	Levomepromazine			X	Testosterone			X
Diclofenac			X	lithium, carbonate	X	X	X	Timolol			X
Digoxin	X	X	X	lorazepam			X	Tiotropium + Olodaterol		X	
diltiazem			X	Losartan potassium	X	X	X	Tirofiban	X	X	
Dimenhydrinate + Pyridoxine, hydrochloride			X	Metformin	X	X	X	Topiramate	X	X	

Dimenhydrinate + Pyridoxine, hydrochloride + Glucose + Fructose			X	Methyldopa	X	X	X	Tramadol			X
Dipyrone	X	X	X	Methylprednisolone	X	X	X	triamcinolone			X
Sodium dipyrone + Promethazine + Adiphenine			X	Metoclopramide	X	X	X	Trihexyphenidyl	X	X	
Donepezil	X	X		Metoprolol, succinate	X	X		tromethamine			X
Doxazosin	X	X	X	Metoprolol tartrate	X	X	X	Umeclidinium + Vilanterol		X	
Enalapril	X	X	X	midazolam	X	X	X	warfarin	X	X	X
enoxaparin sodium	X	X	X	Morphine	X	X	X	verapamil	X	X	
Erythromycin	X	X	X	nalbuphine			X	vigabatrin	X	X	
scopolamine			X	naproxen	X	X		ziprasidone	X	X	
Scopolamine + Sodium dipyrone			X	Neostigmine			X				
Spiramycin	X	X	X	Nifedipine	X	X	X				

*MPI = potentially inappropriate medication for the elderly **RE_{20} = National List of Essential Medicines 2020; ***RE_{22} = National List of Essential Medicines 2022; ****REM = Municipal list of essential medicines for the city of São Paulo 2016; [1] AGS, 2019, [2] O'MAHONY, 2015

Table 1: Potentially Inappropriate Medications for the Elderly identified in REMUME-SP 2016, RENAME 2020 and RENAME 2022, according to Beers 2019[1] and STOPP 2015[2]

ATC Rating	No		
	RE_{20}	RE_{22}	REM
A: Digestive system and metabolismo	10	8	11
B: Blood and hematopoietic organs	7	7	4
C: Cardiovascular system	20	21	23
D: Dermatological drugs	-	-	-
G: Genitourinary system and sex hormones	two	two	4
H: Systemic hormone preparations, excluding sex hormones and insulins	9	9	9
J: Anti-infectives for systemic use	6	6	6
L: Antineoplastic agents and immunomodulators	-	-	-
M: Musculoskeletal system	5	5	7
N: nervous system	42	42	48
Q: Antiparasitic products, insecticides and repellents	-	-	-
A: Respiratory system	4	6	7
S: Sensitive organs	-	-	1
V: Various	-	-	-
TOTAL:	**105**	**106**	**120**

*RE20 = National List of Essential Medicines 2020; **RE_{22} = National List of Essential Medicines 2022; ***REM = Municipal list of essential medicines for the city of São Paulo 2016; [1]AGS, 2019; [2]O'MAHONY, 2015

Table 2: Therapeutic and Chemical Anatomical Classification (ATC) of Potentially Inappropriate Medications for the Elderly (PIMs) in REMUME-SP 2016, RENAME 2020 and RENAME 2022, according to Beers[1] and STOPP[2] instruments

Drugs present in Potential Drug Interactions				
RENAME 2020 and 2022				
Abciximab[2]	Clomipramine[1, 2]	Erythromycin[1]	Iloprost[2]	Primidone[1]
Acetylsalicylic Acid[1, 2]	Clonazepam[1]	Spiramycin[1]	Lamotrigine[1]	Promethazine[1, 2]
Valproic Acid[1]	Clopidogrel[2]	Spironolactone[1, 2]	Levetiracetam[1]	propranolol[2]
Amiodarone[1]	Chlorpromazine[1, 2]	Ethosuximide[1]	Losartan potassium[1, 2]	Quetiapine[1]
Amitriptyline[1, 2]	Clozapine[1, 2]	Phenytoin[1]	Methylprednisolone[1, 2]	Risperidone[1]
Atenolol[2]	Codeine[1]	phenobarbital[1]	Metoprolol[2]	Rivastigmine[2]
Atropine[1, 2]	Haloperidol Decanoate[1]	Fludrocortisone[1, 2]	midazolam[1]	Sacubitril valsartan[1, 2*]
Betamethasone[1, 2]	Dexamethasone[1, 2]	Fluoxetine[1]	Morphine[1]	Sulfamethoxazole + Trimethoprim[1]
Captopril[1, 2]	Dexchlorpheniramine[1, 2]	Dexamethasone, disodium phosphate[1, 2]	Naproxen[1, 2]	Tirofiban[2]
carbamazepine[1]	Diazepam[1]	Furosemide[1]	Nortriptyline[1, 2]	Topiramate[1]
Lithium Carbonate[1]	Digoxin[2]	Gabapentin[1]	Olanzapine[1, 2]	Trihexyphenidyl[1, 2]
Carvedilol[2]	Dipyrone[1, 2]	Galantamine[2]	Paracetamol[1, 2]	Warfarin[1, 2]
Ciprofloxacin[1]	Donepezil[2]	Haloperidol[1]	Pyridostigmine[2]	Verapamil[2]
Clarithromycin[1]	Doxazosin[1]	Hydrocortisone[1, 2]	Prednisolone[1, 2]	vigabatrin[1]
Clobazam[1]	Enalapril[1, 2]	Ibuprofen[1, 2]	Prednisone[1, 2]	Ziprasidone[1]
REMUME-SP 2016				
Acetylsalicylic acid[1, 2]	Clopidogrel[2]	Scopolamine[1, 2]	Lamotrigine[1]	Pindolol[2]
Amiodarone[1]	Chlorpromazine[1, 2]	Spiramycin[1]	Levomepromazine[1]	Prednisolone[1, 2]
Amitriptyline[1, 2]	Clozapine[1, 2]	Spironolactone[1, 2]	Lorazepam[1]	Prednisone[1, 2]
Atenolol[2]	Codeine[1]	Phenytoin[1]	Losartan potassium[1, 2]	Promethazine[1, 2]
Atropine[1, 2]	Dexamethasone[1, 2]	phenobarbital[1]	Methylprednisolone[1, 2]	propranolol[2]
Betamethasone[1, 2]	Dexamethasone, disodium phosphate[1, 2]	sodium phenobarbital[1]	Metoprolol[2]	Quetiapine[1]
Bromazepam[1]	Dexchlorpheniramine[1, 2]	Fentanyl[1]	midazolam[1]	Remifentanil[1]
Captopril[1, 2]	Diazepam[1]	Fluoxetine[1]	Morphine[1]	Risperidone[1]
carbamazepine[1]	Diclofenac[1, 2]	Furosemide[1]	nalbuphine[1]	Sertraline[1]
Lithium Carbonate[1]	Digoxin[2]	Gabapentin[1]	Neostigmine[2]	Sufentanil[1]
Carvedilol[2]	Diltiazem[2]	Haloperidol[1]	Nitrazepam[1]	Sulfamethoxazole + Trimethoprim[1]
Ketoprofen[1, 2]	Dimenhydrinate + Pyridoxine[1, 2]	Haloperidol, decanoate[1]	Nortriptyline[1, 2]	theophylline[1]
Ciprofloxacin[1]	Dimenhydrinate + Pyridoxine, Glic, Frut[1, 2]	Hydrocortisone[1, 2]	Olanzapine[1, 2]	Tramadol[1]
Clarithromycin[1]	Dipyrone[1, 2]	Hydroxyzine[1]	Oxybutynin[1, 2]	Triamcinolone[1, 2]
Clobazam[1]	Doxazosin[1]	Ibuprofen[1, 2]	Paracetamol[1, 2]	Tromethamine [1, 2]
Clomipramine[1, 2]	Enalapril[1, 2]	Imipramine[1, 2]	Pericyzine[1]	Sodium Valproate[1]
Clonazepam[1]	Erythromycin[1]	Indomethacin[1, 2]	Pethidine[1]	Warfarin[1, 2]

*Sacubitril valsartan present exclusively in the National List of Essential Medicines 2022; [1] AGS, 2019; [2] O'MAHONY, 2015

Table 3: Drugs in Potential Drug Interactions in REMUME-SP 2016, RENAME 2020 and RENAME 2022 according to Beers[1] and STOPP[2] instruments

Medicines that must be used with caution in REMUME-SP 2016, RENAME 2020 and 2022						
drug	**Class**	**ATC**	**Rational**	**Observation**	**$RE_{20/22}$**	**REM**
Acetylsalicylic acid	non-steroidal anti-inflammatory	B01AC06	Use with caution in the primary prevention of cardiovascular disease due to increased bleeding risk1	-	X	X
Amitriptyline	ADT	N06AA09	Use with caution as it may exacerbate or cause SIADH or hyponatremia1	Monitor your sodium level closely1	X	X
carbamazepine	anticonvulsant	N03AF01			X	X
Clomipramine	ADT	N06AA04			X	X
Chlorpromazine	antipsychotic	N05AA01			X	X
Clozapine	antipsychotic	N05AH02			X	X
Spironolactone	K-sparing diuretic	C03DA01			X	X
Spironolactone + Hydrochlorothiazide	Association of diuretics	C03DA01 + C03AA03				X
Furosemide	loop diuretic	C03CA01			X	X

Medicines that must be used with caution in RENAME 2020 and REMUME-SP 2016						
drug	**Class**	**ATC**	**Rational**	**Observation**	**$RE_{20/22}$**	**REM**
fluoxetine	SSRIs	N06AB03	Use with caution as it may exacerbate or cause SIADH or hyponatremia1	Monitor your sodium level closely1	X	X
haloperidol	antipsychotic	N05AD01			X	X
haloperidol, decanoate	antipsychotic	N05AD01			X	X
hydrochlorothiazide	thiazide diuretic	C03AA03			X	X
hydroxyzine	antipsychotic	N05BB01				X
imipramine	ADT	N06AA02				X
Levopromazine	antipsychotic	N05AA02				X
lithium, carbonate	antipsychotic	N05AN01			X	X
Nortriptyline	ADT	N06AA10			X	X
olanzapine	antipsychotic	N05AH03			X	X
Pericyzine	antipsychotic	N05AC01				X
quetiapine	antipsychotic	N05AH04			X	X
Risperidone	antipsychotic	N05AX08			X	X
sertraline	SSRIs	N06AB06				X
ziprasidone	antipsychotic	N05AE04			X	
Sulfamethoxazole + Trimethoprim	Sulfonamide	J01EE01	Use with caution, due to the increased risk of hyperkalemia when associated with an ACE inhibitor or angiotensin receptor blocker or with reduced CrCl1	-	X	X

*ATC = Anatomical Chemical Therapeutic Classification **TAD = tricyclic antidepressant ***SSRI = selective serotonin reuptake inhibitor ****RE20/22 = National List of Essential Medicines 2020 and 2022 ***** REM = Municipal List of essential medicines in the city of São Paulo 2016; [1] AGS, 2019

Table 4: Medications that must be used with caution present in REMUME-SP 2016, RENAME 2020 and RENAME 2022

Medicines that must pay attention to the renal function of REMUME-SP 2016, RENAME 2020 and 2022								
drug	**Class**	**ATC**	**Rational**	**beers[1]**	**STOP[2]**	**Recommendation**	**$RE_{20/22}$**	**REM**
Acetylsalicylic acid	non-steroidal anti-inflammatory	N02BA01	Risk of deterioration in renal function if eGFR < 50 mL/min/1.73 m²				X	X
ketoprofen		M01AE03						X
Diclofenac		M01AB05						X
Dipyrone		N02BB02					X	X
Ibuprofen		M01AE01			X	-	X	X
indomethacin		M01AB01						X
naproxen		M01AE02					X	
paracetamol		N02BE01					X	X
tromethamine		M01AB15						X
Ciprofloxacin	Quinolone	J01MA02	Increased risk of CNS effects and tendon rupture if CrCl < 30mL/min	X		reduce dose	X	X
colchicine	Antigota	M04AC01	Gastrointestinal, neuromuscular, and brown bone marrow toxicity if CrCl < 30mL/min	X		reduce dose		X
Digoxin	cardiac glycoside	C01AA05	Risk of long-term toxicity at dose greater than 125 µg/day if eGFR < 30 mL/min/1.73 m²		X	-	X	X
Enoxaparin	antithrombotic	B01AB05	Increased risk of bleeding if CrCl < 30mL/min	X		reduce dose	X	X
Spironolactone	Potassium sparing agent	C03DA01	Potassium increase if CrCl < 30mL/min	X		Avoid	X	X
Gabapentin	anti-epileptic	N03AX12	Adverse CNS reactions if ClCr < 60mL/min	X		reduce dose	X	X
Levetiracetam	anti-epileptic	N03AX14	CNS adverse reactions if CrCl ≤ 80mL/min	X		reduce dose	X	
Metformin	biguanide	A10BA02	Risk of lactic acidosis if eGFR < 30 mL/min/1.73 m²		X	-	X	X
Ranitidine*	H2 Antagonist	A02BA02	Changes in mental status if ClCr < 50mL/min	X		reduce dose	X	X

Medicines that must pay attention to the renal function of REMUME-SP 2016, RENAME 2020 and 2022								
drug	**Class**	**ATC**	**Rational**	**beers[1]**	**STOP[2]**	**Recommendation**	**$RE_{20/22}$**	**REM**
Sulfamethoxazole + Trimethoprim	Sulfonamide	J01EE01	Increased risk of hyperkalemia and worsening of renal function if CrCl < 30mL/min	X		Reduce dose if CrCl 15-29 mL/min. Avoid if CrCl <15 mL/min	X	X

*Ranitidine present exclusively in the National List of Essential Medicines 2020 **ATC = Chemical Therapeutic Anatomical Classification; ***$RE_{20/22}$ = National list of essential medicines 2020 and 2022 ****REM = Municipal list of essential medicines in the city of São Paulo 2016;[1] AGS, 2019, [2] O'MAHONY, 2015

Table 5:Medicines that must pay attention to the renal function of REMUME-SP 2016, RENAME 2020 and RENAME 2022

REFERENCES

1. Closs VE, Schwanke, CHA. A evolução do índice de envelhecimento no Brasil, nas suas regiões e unidades federativas no período de 1970 a 2010. Rev. Bras. Geriatr. Gerontol. 2012;15(3):443-58. https://doi.org/10.1590/S1809-98232012000300006

2. Nasri F. O envelhecimento populacional no Brasil. Einstein. 2008; 6(Suppl1):S4-6. Available from: https://pesquisa.bvsalud.org/portal/resource/pt/lil-516986

3. Chaimowicz F, Barcelos EM, Madureira MDS, Ribeiro MTF. Saúde do idoso. 2nd. ed. Belo Horizonte: NESCON UFMG; 2013. Available from: https://www.nescon.medicina.ufmg.br/biblioteca/imagem/3836.pdf

4. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med. 1991;151(9):1825-1832. PMID: 1888249.

5. Lima TJV, Garbin CAS, Garbin AJI, Sumida DH, Saliba O. Potentially inappropriate medications used by the elderly: prevalence and risk factors in Brazilian care homes. BMC Geriatr. 2013;15:22. https://doi.org/10.1186/1471-2318-13-52

6. 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 [published correction appears in Age Ageing. 2018 May 1;47(3):489]. Age Ageing. 2015;44(2):213-218. https://doi.org/10.1093/ageing/afu145

7. Obreli Neto PR, Cuman RKN. Medicamentos potencialmente inapropriados para idosos e sua presença no SUS: avaliação das listas padronizadas. Rev. Bras. Geriatr. Gerontol. 2011;14(2): 285-289.https://doi.org/10.1590/S1809-98232011000200009

8. Brasil. Ministério da Saúde. Relação Nacional de Medicamentos Essenciais: Rename 2020 [Internet]. Brasília: Ministério da Saúde; 2020 [cited 2022 Fev 28]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/relacao_medicamentos_rename_2020.pdf

9. Brasil. Ministério da Saúde. Relação Nacional de Medicamentos Essenciais: Rename 2022 [Internet]. Brasília: Ministério da Saúde; 2022 [cited 2022 Fev 28]. Available from: https://www.conass.org.br/wp-content/uploads/2022/01/RENAME-2022.pdf

10. São Paulo. Secretaria Municipal da Saúde. Relação Municipal de Medicamentos São Paulo [Internet]. São Paulo: Secretaria Municipal da Saúde; 2016 [cited 2022 Fev 28]. Available from: https://www.prefeitura.sp.gov.br/cidade/secretarias/upload/remune2016.pdf

11. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019;67(4):674-94. https://doi.org/10.1111/jgs.15767

12. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2022 [Internet]. Oslo: 2021 [cited 2022 Fev 28]. Available from: https://www.whocc.no/atc_ddd_index/

13. Varallo FR, Oliveira FM, Mastroianni, PC. Safety assessment of essential medicines for elderly people: a bibliographic survey. Braz. J. Pharm. Sci. 2014;50(2):269-84. https://doi.org/10.1590/S1984-82502014000200006

14. Oliveira MG, Amorim WW, Rodrigues VA, Passos LC. Acesso a medicamentos potencialmente inapropriados em idosos no Brasil. Rev APS. 2011;14(3): 258-65. Available from: https://periodicos.ufjf.br/index.php/aps/article/view/14796

15. Lopes LM, Figueiredo TP, Costa SC, Reis AMM. Utilização de medicamentos potencialmente inapropriados por idosos em domicílio. Ciênc. Saúde Colet. 2016;21(11):3429-38. https://doi.org/10.1590/1413-812320152111.14302015

16. 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. https://doi.org/10.1007/s00228-015-1860-9

17. Hanlon JT, Semla TP, Schmader KE. Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug-Disease Interactions in the Elderly Quality Measures. J Am Geriatr Soc. 2015;63(12):e8-e18. https://doi.org/10.1111/jgs.13807

18. Clyne B, Bradley MC, Hughes CM, et al. Addressing potentially inappropriate prescribing in older patients: development and pilot study of an intervention in primary care (the OPTI-SCRIPT study). BMC Health Serv Res. 2013;13:307. https://doi.org/10.1186/1472-6963-13-307

19. Mann E, Böhmdorfer B, Frühwald T, et al. Potentially inappropriate medication in geriatric patients: the Austrian consensus panel list. Wien Klin Wochenschr. 2012;124(5-6):160-169. https://doi.org/10.1007/s00508-011-0061-5

20. Kim DS, Heo SI, Lee SH. Development of a list of potentially inappropriate drugs for the korean elderly using the delphi method. Healthc Inform Res. 2010;16(4):231-252. https://doi.org/10.4258/hir.2010.16.4.231

21. Mimica Matanović S, Vlahovic-Palcevski V. Potentially inappropriate medications in the elderly: a comprehensive protocol. Eur J Clin Pharmacol. 2012;68(8):1123-1138. https://doi.org/10.1007/s00228-012-1238-1

22. Laroche, M-L, Bouthier F, Merle L, Charmes J-P. Médicaments potentiellement inappropriés aux personnes âgées : intérêt d'une liste adaptée à la pratique médicale française. 2009;30(7):592-601. https://doi.org/10.1016/j.revmed.2008.08.010

23. Poudel A, Ballokova A, Hubbard RE, et al. Algorithm of medication review in frail older people: Focus on minimizing the use of high-risk medications. Geriatr Gerontol Int. 2016;16(9):1002-1013. https://doi.org/10.1111/ggi.12589

24. Kojima T, Mizukami K, Tomita N, et al. Screening Tool for Older Persons' Appropriate Prescriptions for Japanese: Report of the Japan Geriatrics Society Working Group on "Guidelines for medical treatment and its safety in the elderly" [published correction appears in Geriatr Gerontol Int. 2017 Feb;17 (2):363]. Geriatr Gerontol Int. 2016;16(9):983-1001. https://doi.org/10.1111/ggi.12890

25. Marzi MM, Pires MS, Quaglia NB. Ingredientes Farmacéuticos Activos Potencialmente Inapropiados en Adultos Mayores: Lista IFAsPIAM: Panel de Consenso Argentino. Value Health Reg Issues. 2018;17:38-55. https://doi.org/10.1016/j.vhri.2017.10.002

26. Zhang H, Wong EL, Yeoh EK, Ma BH. Development of an explicit tool assessing potentially inappropriate medication use in Hong Kong elder patients. BMC Geriatr. 2021;21(1):98. https://doi.org/10.1186/s12877-021-02024-0

27. Pagès A, Mazon M, Cool C, et al. Cost analysis of potentially inappropriate medication in older hospitalized patients. Expert Rev Pharmacoecon Outcomes Res. 2020;20(6):623-627. https://doi.org/10.1080/14737167.2020.1678384

28.Forgerini M, Schiavo G, Lucchetta RC, Mastroianni PC. Drug interactions for elderly people with mental and behavioral disorders: a systematic scoping review. Arch Gerontol Geriatr. 2021;93:104283. https://doi.org/10.1016/j.archger.2020.104283

29. Tommelein E, Petrovic M, Somers A, Mehuys E, van der Cammen T, Boussery K. Older patients' prescriptions screening in the community pharmacy: development of the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP^{3}S) tool. J Public Health (Oxf). 2016;38(2):e158-e170. https://doi.org/10.1093/pubmed/fdv090

30. Prasert V, Shono A, Chanjaruporn F, et al. Effect of a computerized decision support system on potentially inappropriate medication prescriptions for elderly patients in Thailand. J Eval Clin Pract. 2019;25(3):514-520. https://doi.org/10.1111/jep.13065