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Falls Associated With Drug Therapy: An Analysis of The Most Prevalent Chronic Non-Communicable Disease's Treatments in Brazilian Elderly

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ABSTRACT

The three most prevalent chronic non-communicable diseases (NCDs) in the elderly in Brazil are: Systemic Arterial Hypertension (SAH [50.65%]), Diabetes Mellitus (DM [18.10%]) and Arthritis and Rheumatism (16, 43%) The drugs most indicated for their treatments in the elderly were classified and analyzed according to the degree of risk of falls. It is concluded that their uses can favor the occurrence of falls in the elderly.

Keywords
Falls, Pharmacotherapy, Elderly.

Introduction

Falls can be defined as an unintentional change in body position that causes the individual to suffer an impact against the floor or a lower level [1]. In 2018 alone, approximately, 130,000 elderly people were hospitalized in Brazil due to falls [2] and 50% of falls cause injuries, many of which leave sequelae and impaired functionality [3].

Given this scenario, falls in the elderly are now considered a public health problem [1]. Thus, it is necessary to investigate their causes in depth so that interventions capable of preventing them can be proposed. They are caused by a set of risk factors, among which are the practice of polypharmacy and the use of specific medications [3,4].

Amid the drugs that are known to increase the Risk of Falls (RF) in the elderly, opioids, drugs for the treatment of cardiovascular diseases and psychotropic drugs such as antipsychotics, hypnotics and antidepressants stand out [5].

However, there are few studies about whether other drugs can also increase the RF or that investigate the intensity with which the drugs most consumed by Brazilian elderly people can contribute to the increase in the RF, with more common studies that indicate the risk linked to the therapeutic class and not to a specific drug.

Thus, this work aimed to define which are the most prevalent diseases in the elderly in Brazil, identify the ten widely used drugs in their treatment and classify them according to the RF, considering their effects on the body and the comparative analysis of the information available in medicine package leaflets and in the *Drugs.com* and *MedSUS* databases. This study breaks new ground by providing a more objective assessment of the relationship between RF and each drug individually, not just its class.

Method

The *System of Health Indicators and Monitoring of Policies for the Elderly* (SISAP-Idoso) provides a series of statistical data on the Brazilian elderly population, including the indicator "Proportion of elderly people with some chronic non-transmissible disease" (P), which in turn was used to determine the most common non-transmissible chronic diseases (NCDs) in old age [6]. The proportion in percentage was calculated for each NCD available in SISAP-Idoso as follows (1):

P determination (1)

$$P = \frac{\text{Number of elderly people who declared having received a medical diagnosis of a chronic disease}}{\text{Estimated elderly population}} \times 100$$
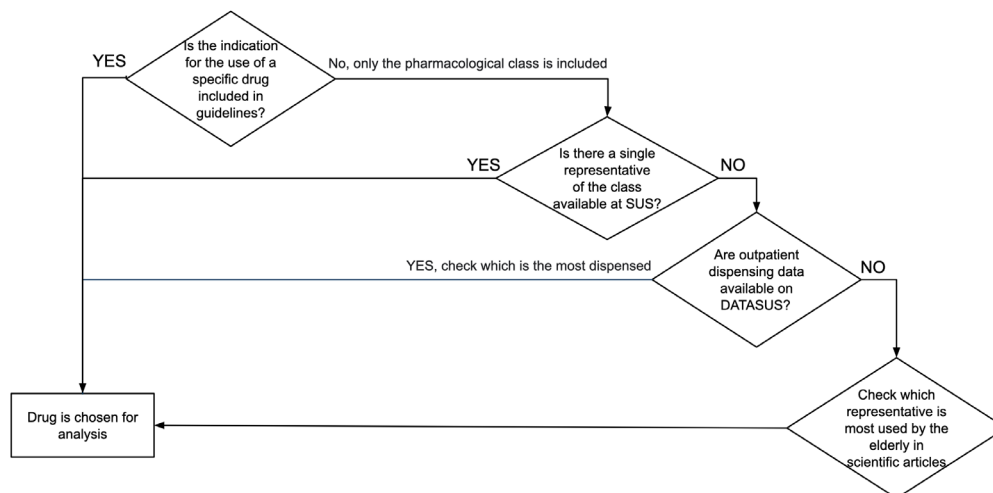

Figure 1: Flowchart with the hierarchical criteria for defining the drug to be analyzed. (Source: Authors, 2022)

In order to determine the ten drugs to be analyzed, the therapeutic regimens for the treatment of the three most prevalent NCDs, available in the Clinical Protocols and Therapeutic Guidelines (Protocolos Clínicos e Diretrizes Terapeuticas - PCDT) and/or in the guidelines for each disease, were examined. For cases in which the PCDT indicate only the pharmacological class, their representatives available in the Unified Health System (Sistema Único de Saúde - SUS) were considered for analysis. In case of availability of more than one drug of the same class in the SUS, the criteria described in Figure 1 were used to define which drug of the indicated class would be analyzed:

The determination of the Degree of Risk of Falls (DRF) of each drug was based on the following 14 adverse drug reactions (ADRs) as a risk for the occurrence of falls: 1-Orthostatic hypotension; 2-Arterial hypotension; 3-Arterial hypertension; 4- Bradycardia; 5-Psychomotor agitation; 6-Mental confusion; 7- Dizziness; 8-Drowsiness or sedation; 9-Decreased vision; 10-Seizures; 11-Atony, dystonia or muscle weakness; 12-Hypoglycemia; 13-Urgency in urination and 14-Diarrhea or urgency in defecation [7].

To verify whether each medication causes these RF and ADRs, the medicine package leaflet, the *MedSUS®* application and *Drugs. com®* were consulted. Only ADRs occurring at recommended doses and described as very common (Frequency ≥ 10%), common (10%>Frequency ≥ 1%) or uncommon (1%>Frequency≥ 0.1%) [8] were included.

Thus, each RF effect present was assigned one point to the drug [7], resulting in the following possible classifications: *DRF 0: drug without RF factors; DRF I: 1 to 2 factors (low risk); DRF II: 3 to 5 factors (intermediate risk I); DRF III: 6 to 9 factors (intermediate risk II); DRF IV: 10 to 14 factors (high risk).* All data were entered and analyzed in the Microsoft® Office Excel 2016® program for descriptive analysis.

The Micromedex® Drug Interactions database was consulted to verify if the 10 selected drugs have drug interactions (DI) that offer RF. Drug interactions of moderate, severe or contraindicated severity were considered.

The epidemiological information used in this study was collected between January and October 2020. According to Law 10,741/2003, a person aged 60 years or older is considered elderly [9]. Thus, information referring to other age groups, other countries, and data on non-chronic diseases or those treated with non-pharmacological therapies were excluded. There was no need for submission to the Institutional review board.

Results
Determination of the Most Prevalent Diseases in the Elderly in Brazil
The Table 1 presents the five most frequent NCDs in Brazilian elderly: systemic arterial hypertension (SAH), cataracts, chronic back problems (CBP), diabetes mellitus (DM) and arthritis or rheumatism [6].

Table 1: Proportion of elderly diagnosed by disease. Data expressed in percentage.

Disease	Proportion of elderly people diagnosed (%)
1. Systemic arterial hypertension	50,65
2. Cataracts in one or both eyes	28,67
3. Chronic back problem	28,10
4. Diabetes mellitus	18,10
5. Arthritis or rheumatism	16,43
Proportion of elderly people with a NCD	**76,30**

Source: SISAP-Idoso, 2018 [2].

Therapies for cataracts and CBP were ruled out, as their most recommended treatments are non-pharmacological [10,11].

The popular term "rheumatism" refers to a set of different diseases, which mainly affect the locomotor system [12]. Among them is rheumatoid arthritis (RA), which, as it is highlighted in the indicator, was the rheumatic disease chosen for analysis. Therefore, the drugs used for the treatment of SAH, DM and RA were evaluated in terms of RF.

Drugs used for the treatment of SAH
For the initial choice of monotherapy for SAH, the use of thiazide diuretics (TDs), angiotensin-converting enzyme inhibitors (ACEI), calcium channel antagonists (CCA) and angiotensin receptor blockers (ARB) is preferably recommended [13].

Furthermore, Mengue et al., 2016 evaluated the use and access to drugs for the treatment of SAH among a sample of diagnosed Brazilians. In descending order, the five most used drugs were: hydrochlorothiazide (used in 23.9% of patients, 95%CI 22.7-25.1), losartan (used in 20.1% of patients, 95%CI 19.0- 21.3), captopril (11.2%, 95%CI 10.2-12.2), enalapril (10.5%, 95%CI 9.4-11.7) and atenolol (9.0%, 95%CI 8.2-9.9) [14].

Therefore, the three antihypertensives chosen for analysis regarding the RF are: hydrochlorothiazide (TD), losartan (ARB II) and captopril (ACEI).

Drugs used for the Treatment of DM
Metformin hydrochloride is the first choice pharmacological treatment for type 2 DM (DM2). However, approximately half of people start using one more medication after two years of starting treatment with metformin.

Thus, it is customary to associate a sulfonurea, the most economically accessible class after metformin [15]. The sulfonureas dispensed by the SUS are gliclazide and glibenclamide [16], with the use of gliclazide being preferred, since, as it is the latest generation, it presents better tolerability and a lower risk of hypoglycemia, ADR that is especially worrying in the elderly [15].

When a third medication is necessary, intermediate or long-acting insulins are used. In the SUS, intermediate-acting insulin (Neutral Protamine Hagedorn – NPH) is available [16]. Thus, the three antidiabetics of choice are: metformin, gliclazide and NPH insulin.

Medications used for the Treatment of RA
Methotrexate, a conventional synthetic disease-modifying drug (scDMARD), is the drug of first choice for RA [17].

If disease activity persists, a biological disease-modifying drug can be added as a second line of treatment [17]. There are eight MMCDbio available in the SUS, with etanercept 50mg being the most dispensed [18]. The use of glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) is also recommended for the symptomatic control of RA [17]. The two NSAIDs available on the SUS are ibuprofen and naproxen (Ministério da Saúde, 2020). As the half-life of naproxen is longer, its dosage is more convenient [17].

Regarding glucocorticoids, the use of prednisone or prednisolone is recommended, both dispensed by the SUS (Ministério da Saúde, 2020). Prednisone is usually used more, as it is in the pharmaceutical form of tablets, while prednisolone is an oral solution [17].

Thus, methotrexate, etanercept, naproxen and prednisone are the RA drugs chosen for analysis.

Analysis of the Relationship between Medications and the Potential Increase in RF
All ten drugs included for analysis in this study were classified according to DRF according to the information about their effects or ADRs present in the medicine package leaflet, on Drugs.com® and MedSUS®. Thus, three different classifications were generated, each originating from one of the three research sources, which will be analyzed and compared below. The maximum possible score is 14 points and the highest DRF is IV [17]. Chart 1 has all RF ADRs identified for each drug and their total scores.

Only the classification from the medicine package leaflet presented a drug considered DRF 0 (etanercept) [19] and a DRF IV (gliclazide) [20,21] (Table 2). In the three rankings, etanercept always appears in last place, with a total score varying between 0 and 2 (Table 3), which suggests that it does not offer RF.

Table 2: Number of drugs by degree of risk of falls according to the source of consultation used. Data expressed in absolute values and percentage.

Degree of risk of falls	Medicine Package Leaflet		Drugs.com		MedSUS	
	n	%	n	%	n	%
0	1	10%	0	0	0	0
I	1	10%	2	20%	1	10%
II	4	40%	5	50%	7	70%
III	3	30%	3	30%	2	20%
IV	1	10%	0	0	0	0

On the other hand, gliclazide, which was the drug with the highest total score according to the medicine package leaflet (11 points; DRF IV) [20,21], obtained only 4 points (DRF II) both in the Drugs.com® and of MedSUS (Table 3). This great difference was due to the fact that the gliclazide medicine package leaflet thoroughly describes the symptoms of hypoglycemia, which are individually scored as RF factors, such as bradycardia, seizures and muscle weakness (Chart 1) [20,21]. MedSUS and Drugs.com® do not detail the consequences of hypoglycemia, resulting in a lower score.

The pattern of non-detailing of the signs of sudden reduction in glycemia is maintained in MedSUS in relation to NPH insulin (3 points; DRF II) (Chart 1). Drugs.com®, on the other hand, listed the highest amount of ADRs this time, resulting in seven points for NPH insulin (DRF III), against the 5 derivatives on the medicine package leaflet [22] (DRF II) (Table 3).

Table 3: Classification of drugs according to the risk of falls. Data in descending order and ranked according to the query source used.

Database	Ranking	Drug	Score	DRF
Medicine Package Leaflet	1º	Gliclazide	11	IV
	2º	Hydrochlorothiazide	6	III
		Losartan	6	III
		Methotrexate	6	III
	5º	NPH Insulin	5	II
		Prednisone	5	II
	7º	Captopril	4	II
		Naproxen	4	II
	9º	Metformin	1	I
	10º	Etanercept	0	0
Drugs.com	1º	Hydrochlorothiazide	8	III
	2º	NPH Insulin	7	III
	3º	Losartan	6	III
	4º	Methotrexate	5	II
		Naproxen	5	II
	6º	Prednisone	4	II
		Gliclazide	4	II
	8º	Captopril	3	II
	9º	Metformin	2	I
		Etanercept	2	I
MedSUS	1º	Losartan	6	III
		Methotrexate	6	III
	3º	Naproxen	5	II
	4º	Gliclazide	4	II
		Hydrochlorothiazide	4	II
		Prednisone	4	II
		Captopril	4	II
	8º	NPH Insulin	3	II
		Metformin	3	II
	10º	Etanercept	1	I

Among the three antidiabetics, metformin had the lowest score, ranging from 1 to 3 points (Table 3). This is probably because the most common ADR for the representative of biguanides is diarrhea [23-25] unlike the others, who have hypoglycemia as their main ADR [20-22], which not only reinforces the significant relationship between hypoglycemia and RF potentiation, but also suggests metformin as the safest antidiabetic drug in terms of RF.

Regarding antihypertensive drugs, the drug that offers the lowest RF is captopril (DRF II) [26] (Table 3). Antihypertensive drugs usually have common RF effects that are related to a decrease in blood pressure (BP), such as dizziness and orthostatic hypotension [26-28]. The difference in classification regarding the DRF between them, however, can be explained by intrinsic particularities of hydrochlorothiazide and losartan.

Losartan differs, as hypoglycemia is one of its common ADRs [27], while hydrochlorothiazide differs by increasing urinary frequency [28]. As the patient gets up more often to urinate, the use of hydrochlorothiazide can increase ambulation, favoring the RF and obtaining DRF III in two of the classifications (Table 3).

Among the drugs involved in the treatment of RA, prednisone and naproxen were classified as DRF II and methotrexate as DRF III in two of the classifications (Table 3).

High blood pressure and decreased vision were risk effects linked to prednisone in all three databases (Medsus) (Drugs.com®) [29]. Furthermore, more than half of naproxen RF ADRs are present in the three references [30] (Table 1). This coherence between the information indicates a good degree of security in relation to the veracity of the data.

Comparing the three general classifications with each other, 100% (10) of the drugs were classified with the same DRF in at least two consultation sources. However, only 40% (4) of the drugs obtained the same classification in all three databases. They are losartan, captopril, prednisone and naproxen. Losartan was the only one that obtained the exact same score (6 points) in the three sources (Chart 1).

Only gliclazide had a significant difference of two degrees between the classifications (DRF IV in the medicine package leaflet and DRF II in the others), so that for the other drugs, the difference, if any, was only one degree. Despite this, no medicine presented exactly the same list of ADRs in the three databases, which shows a difference in the level of detail and type of information available in each source (Chart 1).

For drugs with DRF greater than or equal to II, it was found that MedSUS and its medicine package leaflets do not inform that the drug can exacerbate RF in the elderly [20-27,29-31] and the only drug that Drugs.com® explicitly reports can cause falls is losartan. The lack of this information makes it difficult to properly prescribe medications regarding the RF, since the health professional and the patient do not have access to the information.

Therefore, it is worth noting that dizziness, arterial and postural hypotension and mental confusion are factors that can cause falls [7], but that also affect activities that require attention, such as the ability to drive and operate machines [27].

Thus, although the RF is not included in any medicine package leaflet, the medicine package leaflets of 5 of the 9 drugs with significant DRF indicate that the use of the drug impacts the ability to drive and operate machines or recommend caution when carrying out these activities in treatment. They are hydrochlorothiazide, losartan, gliclazide, NPH insulin and naproxen [20-23,27,28,30]. Because they have common risk factors among themselves, our group proposes that the RF, which currently does not exist in medicine package leaflets, be notified together with the caution when driving and operating machines.

Drug Interactions

Seventeen DIs were identified among the ten drugs under review, of which five are considered severe and 12 moderate [32]. Of the total, 11 DIs are related to increased RF by exacerbating risk

Chart 1: Presence of adverse reactions that increase the risk of falls according to the medicine package leaflet for each drug, *Drugs.com®* and *MedSUS*.

Disease	Drug	Presence of Effects Capable of Favoring the Risk of Falls Due to Medication		
		Medicine Package Leaflet	Drugs.com®	MedSUS
SAH	Hydrochlorothiazide	Arterial Hypotension		
		Dizziness		
		Vision decrease		
		Diarrhea or urgency to defecate		
		Urination urgency		
		Atony, Dystonia or Muscle Weakness		-
			Mental Confusion	
		-	Seizures	
	Total Score	**6**	**8**	**4**
	Risk Degree	**III**	**III**	**II**
	Losartan	Orthostatic Hypotension		
		Arterial Hypotension		
		Dizziness		
		Hypoglycemia		
		Diarrhea or urgency to defecate		
		Drowsiness or Sedation		Atony, Dystonia or Muscle Weakness
	Total Score	**6**	**6**	**6**
	Risk Degree	**III**	**III**	**III**
	Captopril	Arterial Hypotension		
		Diarrhea or urgency to defecate		
		Dizziness		Orthostatic Hypotension
		Orthostatic Hypotension	-	Seizures
	Total Score	**4**	**3**	**4**
	Risk Degree	**II**	**II**	**II**
DM	Metformin	Diarrhea or urgency to defecate		
			Hypoglycemia	
		-	-	Dizziness
	Total Score	**1**	**2**	**3**
	Risk Degree	**I**	**I**	**III**
	Gliclazide	Diarrhea or urgency to defecate		
		Hypoglycemia		
		Drowsiness or Sedation		Arterial Hypertension
		Vision decrease		Dizziness
		Psychomotor Agitation	-	-
		Mental Confusion	-	-
		Dizziness		
		Bradycardia		
		Seizures	-	-
		Atony, Dystonia or Muscle Weakness		
		Arterial Hypertension		
	Total Score	**11**	**4**	**4**
	Risk Degree	**IV**	**II**	**II**
	NPH Insulin	Mental Confusion		
		Hypoglycemia		
		Vision Decrease		
		Atony, Dystonia or Muscle Weakness		
		Drowsiness or Sedation		-
		-	Dizziness	-
			Arterial Hypotension	
	Total Score	**5**	**7**	**3**
	Risk Degree	**II**	**III**	**II**

RA				
	Methotrexate	Diarrhea or urgency to defecate		
		Dizziness		
		Seizures		
		Vision decrease	Drowsiness or Sedation	
		Mental Confusion		Vision decrease
		Arterial Hypotension	-	Arterial Hypotension
	Total Score	6	5	6
	Risk Degree	III	II	III
	Etanercept	Does not have an effect on the risk of falls	Dizziness	Seizures
			Diarrhea or urgency to defecate	-
	Total Score	0	2	1
	Risk Degree	0	I	I
	Prednisone	Arterial Hypotension		
		Vision decrease		
		Arterial Hypotension	Psychomotor Agitation	Bradycardia
		Seizures	Dizziness	Seizures
		Atony, Dystonia or Muscle Weakness	-	-
	Total Score	5	4	4
	Risk Degree	II	II	II
	Naproxen	Dizziness		
		Drowsiness or Sedation		
		Diarrhea or urgency to defecate		
		Vision decrease		Arterial Hypertension
		-	Mental Confusion	Hypoglycemia
	Total Score	4	5	5
	Risk Degree	II	II	II

effects, such as hypoglycemia (55% of DIs), changes in BP (36%) and reduced diuretic efficacy (9%) (Chart 2), which increases RF by leading to uncontrolled BP.

Chart 2: Drug interactions capable of increasing the risk of falls in the elderly, their respective severities and effects. Data analyzed using the Micromedex® Drug Interactions® platform.

Drug Interaction	Severity	Effect
Metformin or Gliclazide + NPH Insulin	Moderate	Increased risk of hypoglycemia
Metformin or Gliclazide + Captopril	Moderate	
Losartan + NPH Insulin	Moderate	
Captopril + NPH Insulin	Moderate	
Losartan + Captopril	Severe	Increased risk of ADRs, such as low blood pressure
Hydrochlorothiazide + Captopril	Moderate	Excessive BP reduction
Captopril + Naproxen	Moderate	May increase BP
Losartan + Naproxen	Moderate	
Hydrochlorothiazide + Naproxen	Severe	Decreased diuretic effectiveness

Discussion

The high prevalence of NCDs in old age and the common use of more than one medication for their treatment contribute to the increase in the RF, since the use of four or more medications at the same time is proven associated with favoring the occurrence of falls [33].

Therefore, it is especially important to adopt a model of care centered on the person and not on the disease in cases of elderly patients who are frail or use many combined medications. In this model, an attempt is made to analyze how the patient's illnesses are interrelated and affect their quality of life, which avoids excessive medicalization, promotes the management of DIs and a closer look at ADRs [34], which can decrease the occurrence of falls.

In this way, the review of medical prescriptions for hospitalized patients and the inclusion of clinical pharmacists in the multidisciplinary team also decrease the RF and increase patient safety [35]. The pharmacist, along with the multidisciplinary health team, must use appropriate strategies for the prevention of falls, such as suggesting lower-risk therapeutic alternatives to the prescriber, providing guidance on the rational use of medications and encouraging reporting of falls [36].

Comparing the DRF data found in this study with the literature, there is agreement in relation to antihypertensive drugs, and our results indicate DRF II or III, intermediate RF. The "Johns Hopkins Fall Risk Assessment Scale (JH-FRAT)" also classifies the use of 2 antihypertensive drugs by the elderly as of intermediate RF [37]. In addition, the Scottish guide "Polipharmacy Guidance Realistic Prescribing" categorizes TDs, ACE inhibitors and ARB II as having moderate RF [38,39].

There is also agreement regarding antidiabetic agents, as the bulletin "Medicines associated with the occurrence of falls" recommends that the use of antidiabetic agents and IM that favor the risk of hypoglycemia be evaluated as a strategy to reduce the occurrence of medication-related falls [5]. Also, a study carried out in Canada found that hypoglycemic agents were the 4th class

of medications most associated with falls (13.6% of cases), behind only opioids, psychotropics and cardiac medications [40].

Naproxen has been classified as intermediate risk (DRF II) and there are some studies that also suggest an association between NSAID use and increased RF in the elderly [41]. Another article, a meta-analysis developed at the University of Amsterdam, demonstrates that 6 out of 26 studies suggest a positive relationship between the use of NSAIDs and the occurrence of falls [42].

Although methotrexate and prednisone result in intermediate DRF, no significant data were found in the literature about the relationship between the use of these drugs and RF. Many drugs currently not widely regarded as RF, such as NSAIDs, methotrexate, and glucocorticoids, are only addressed in a few studies, which are sometimes of poor quality. Thus, it is likely that there are other yet unidentified RF drugs [42].

In addition, the comparison of the scores used to define the DRF of each drug makes it possible to suggest a profile for each database: *MedSUS* presented the highest number of DRF II classifications (3-5 points), as there is not much detail about the ADR on this base. This can possibly be explained by the fact that *MedSUS* is an application, an easily accessible tool that tends to have the intention of passing on the necessary information succinctly and quickly.

The *Drugs.com*® classifications are concentrated more homogeneously between grades I, II and III (20%, 50% and 30%, respectively, Table 2), which indicates a profile of detail that varies from intermediate to high.

Finally, the medicine package leaflets showed greater discrepancy among themselves, with very detailed medicine package leaflets being found, such as that for gliclazide [20,21], and other more succinct ones, such as etanercept [19] and metformin [23-25], which obtained the lowest total scores. This discrepancy probably occurs because the medicine package leaflets are not all written by the same group of authors, varying greatly from laboratory to laboratory, which interferes with the quality of information.

Conclusion
Drugs commonly used for the treatment of systemic arterial hypertension, diabetes mellitus and rheumatoid arthritis in the elderly may favor the occurrence of falls, even with different degrees of risk and especially when used in combination. However, there are few consistent data in the literature on the relationship between the use of non-steroidal anti-inflammatory drugs, glucocorticoids, methotrexate and the risk of falls. Therefore, it is necessary to develop new studies focused on the analysis of drugs with the potential to increase the risk of falls and which have not yet been classified as such.

Possible strategies to promote prevention and awareness about the use of medications and the increased risk of falls are:

a- The inclusion in medicine package leaflets of explicit information that a medication can increase the risk of falls in the elderly

b- Valuing the role of the clinical pharmacist and the review of the patient's pharmacotherapy, with the aim of avoiding polypharmacy and managing drug interactions that may increase the risk of falls.

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