End of degree project
Degree in Medicine

Relationship between polypharmacy and potentially inappropriate prescription in patients over 65 in a Spanish rural area. A comparison of STOPP and Beers criteria

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Leioa, April 2, 2017

AGRADECIMIENTOS

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1. INTRODUCTION

The increase in life expectancy along with the low birth rate of most countries is making the world's older population grow [1]. For this reason we are giving more importance to the quality, quantity and safety of the drugs that are prescribed to the elderly. Studies in this field have become more important in recent years.

1.1. POLYPHARMACY

Polypharmacy is a prevalent problem among the population over 65 years of age and has important consequences in the outcome of the patient, who is already suffering structural and functional changes, such as a reduction in their the homeostatic capacity. And in general their sensitivity to the drugs is increased [2]. This excess of medication is associated with problems like adherence to the treatment, interactions between drugs and adverse reactions.

There is no agreement to define the polymedicated patient. The vast majority of the definitions use a quantitative point of view, focusing on the number of prescribed drugs [3]. It can be also defined qualitatively, so the patient will be assigned different degrees of polypharmacy according to the number of drugs they consume [4]. However, most of the literature agrees to use the quantitative definition. The most commonly used description dictates that the polymedicated patient is the one that takes more than 6 medications over a period of time of at least 6 months [5].

Aside from the health problems that may arise from the polypharmacy, there is also an economic impact, both to the patient and the administration. This is due to greater number of consultations, more personal required and the adverse drug effects associated with their treatment [6].

1.2. POTENTIALLY INAPPROPRIATE PRESCRIPTION

Recent reviews have pointed out that the problem is not polypharmacy but inappropriate prescription, and suggest that this is the problem that must be addressed to optimize pharmacotherapy in older people [7-10]. An Irish 2015 study claims that polypharmacy is the main factor of exposure to inappropriate prescription. However, they point out that physicians are prescribing more

appropriately nowadays and despite the marked increase in polypharmacy, inappropriate prescription is not growing at an alarming rate [11].

A drug is considered adequate when evidence-based medicine supports its use in a particular case when it is well tolerated by the majority of patients and its cost-effective. We must also keep in mind the individual life expectancy of each person avoiding this way preventive therapies in patients with and unfavorable shot-term prognosis and promote drugs with a good benefit/risk ratio [12].

Inappropriate prescription of drug includes: medication used when the risk of adverse reactions outweights clinical benefit (especially if there is a safer or more effective alternative) [13], the omission of indicated drugs in the absence of contraindications when the patient has a significant life expectancy, when a drug is given at a frequency higher that indicated or when medications that interact between each other or with the diseases of the patient are prescribed [14]. This is more common in elderly patients [15, 16] and associated with adverse effects [17]. It is significantly related to hospitalization, functional impairment, avoidable resource utilization and death [18, 19, 20, 21, 22].

The health problem this is causing should not be ignored, several studies show that 17.5% to 23.5% of community-dwelling older adults take at least one drug that could be considered inappropriate [23]. The use of these medications can have serious consequences for the health of the patients besides being bad for the administration too [24].

1.3. TOOLS FOR DETECTING INAPPROPIATRE PRECRIPTION

Different types of tools for analyzing inappropriate prescriptions have been developed with the aim of guiding physicians in clinical practice. Some examples of them would be STOPP, Beers and Taiwan criteria as well as the EU(7)PIM. Most of them conclude that the two with a more balanced profile are the STOPP and Beers' criteria [25].

Beers' criteria were first described in 1991 [26]. They were originally developed to detect inappropriate prescriptions in nursing homes of the United States and consisted on a list of thirty drugs that should be avoided. In subsequent reviews

(1997, 2003 and 2012) new medications were added according to specific pathologies. [27]. The last modification was carried out by the American Geriatrics Society in 2015, where an interdisciplinary committee of 13 experts met and applied the Delphi method [66] to include new drugs. They added new medications, incorporated new areas of interactions and graduated the quality of each inappropriate prescription based on the level of evidence [28].

The STOPP (Screening Tool of Older Person's Prescriptions) criteria were born in Ireland in 2008 and its clinical development was carried out by the European Union Geriatric Medicine Society. They describe the most common treatment errors in prescriptions of older adults. STOPP criteria are easy to relate to a diagnosis since they are grouped by physiological systems and can be integrated into prescription computer systems. Unlike Beers' criteria, STOPP has a list that detects the lack of prescription when a medication is potentially indicated (START). Its last revision was carried out in 2014 by a committee of 19 experts in geriatrics and geriatric pharmacologists of 13 European countries, they used the Delphi method for the validation of new norms. Fifteen criteria were excluded because there were not enough evidence to support them and 24 were added (12 to STOPP and 12 to START) [29].

1.4. COMPARISONS BETWEEN BEERS AND STOPP CRITERIA

Several studies compare both criteria, [30, 31, 32, 33] however the continuous reviews of both [28, 29] may the reason why there is limited literature analyzing their last two versions. In the United States Beers' criteria are used frequently to detect inappropriate prescription [35, 36] and studies show a clear benefit of their application [37]. None the less their efficacy still generates controversy in European countries since some of the drugs included are not prescribed or even available in these countries [34].

Despite the discrepancies, comparisons of different studies show a prevalence of inappropriate prescription between 38 and 45% when using the STOPP criteria and between 20 and 35% after the application of Beers' criteria [30, 31, 32, 33, 38]. STOPP criteria has been officially translated to several languages [39] which is an advantage against Beers' criteria, where we can find less independent adaptations.

An example of such would be a study that excludes some of the drugs not available in Europe and includes others with the same profile that are usually administrated in this region [40]. Ultimately, we believe that the future lies on the computerization of these criteria because it could be helpful for physicians when making clinical decisions [41].

2. OBJECTIVES

This investigation studied polypharmacy and its relation to inappropriate prescription, with three main objectives:

1. Get to know the prevalence of potentially inappropriate prescription in patients over 65 in a rural area applying STOPP and Beers' criteria to their chronic medication.

2. Measure the degree of agreement between STOPP (version 2) [Appendix A] and Beers (2015 review) [Appendix B] criteria to detect potentially inappropriate prescription (PIP)

3. Determine the association between polypharmacy and PIP.

3. MATERIALS AND METHODS

3.1. TYPE OF STUDY

An observational cross-sectional study.

3.2. STUDY POPULATION

This research was carried out in a rural area of A Coruña, located in the northwest of Spain. The Health Center is in charge of 12,057 people of which 3,344 are over 65. Patients over 99, hospitalized, in palliative care or in nursing homes were excluded from the study.

In order to achieve a precision of 5% in our estimation using a confidence interval of 95%, assuming that the proportion is 50% it was necessary to include 385 experimental units in the study, however 34 patients were excluded, so we assume that our precision is 5,2%.

3.3. SOURCES OF INFORMATION

Data were collected through electronic medical records using the Galician Health Service (SERGAS) IANUS system between January 1 and March 12, 2017. This information included gender, age, comorbidities, latest blood tests, other complementary studies and active medication. The 351 participants were randomly selected from the 3.344 patients of the Health Centre. In this study the polypharmacy patient was defined as one who takes six or more drugs for a period of time equal or greater than six months [5].

A database was made including gender, age, active chronic medication, relevant blood tests and chronic pathologies of each patient in order to apply STOPP or Beers' criteria. We only included drugs that the patients bought since IANUS system allows to check if the prescribed medication have been dispensed or not.

In order to detect PIP, STOPP (version 2) [Appendix A] and Beers' criteria (2015 review) [Appendix B] were applied.

3.4. ANALYSIS

A descriptive analysis about the characteristics of the study population was made, distributing by gender, age and number of prescribed chronic medications. STOPP and Beers' criteria were applied and prevalence of PIP was calculated. These were only applied to chronic medication, acute medication was not included in this study.

On the one hand, to measure the degree of agreement between STOPP and Beers' criteria the Cohen kappa index and the intraclass correlation coefficient (ICC) were used. To evaluate the K statistic, we followed the classification proposed by Landis and Koch [42], which establishes that a K that equals 1 is a perfect agreement, more than 0,81 indicates an almost perfect agreement, between 0,61 and 0,80 substantial, between 0,41 and 0,60 moderate, between 0,21 and 0,40 fair, between 0, and 0,20 slight and less than 0 poor. For the interpretation of the ICC we followed the classification proposed by Landis and Kock (1977) according to which a ICC that equals 1 is a perfect agreement, more than 0,81 indicates an almost perfect agreement, between 0,61 and 0,80 substantial, between 0,41 and 0,60 moderate, between 0,21 and 0,40 fair, between 0, and 0,20 slight and less than 0 poor

On the other hand, in order to calculate the correlation between the number of prescribed chronic drugs and PIP, we used the Spearman's rho coefficient since the distribution of the number of medications was very asymmetric. This was interpreted by the following classification: a Spearman correlation coefficient of more than 0,75 indicates a very strong connection, between 0,40 and 0,75 strong, between 0,25 and 0,40 moderate, between 0,15 and 0,24 weak and less than 0,15 very weak.

4. RESULTS

Data were collected from 351 randomized patients of which 207 (59%) were women (Table 1). The mean age (interquartile range) was 75 (68-81) and the range of ages from 65 to 99. A total of 1252 prescriptions were analyzed and the groups according to the quantity of chronic drugs taken were significantly homogenous with the highest concentration of patients in the range of 2 to 3 medications, 104 (30%). The number of polymedicated patients according to our definition is 81 (23%).

Table 1. Characteristics of the study population (n=351)

	Male	Female	Total
Number of patients	144 (41%)	207 (59%)	351
Age distribution (years)			
Median age (IQR)	73 (68-81)	75 (68-81)	75 (68-81)
65-74	81 (47%)	91 (53%)	172 (49%)
75-84	42 (33%)	24 (53%)	45 (13%)
85-94	21 (47%)	24 (53%)	45 (13%)
+95	0 (0%)	5 (100%)	5 (1%)
Number of chronic drugs prescribed			
1 or less	32 (41%)	47 (59%)	79 (23%)
2 to 3	39 (38%)	65 (63%)	104 (30%)
4 to 5	44 (51%)	43 (49%)	87 (25%)
More than 6	28 (35%)	53 (65%)	81 (23%)

IQR = Interquartile range

4.1. POTENTIALLY INAPPROPRIATE PRESCRIPTIONS

One hundred and fifty-four STOPP criteria were breached among 34% (n=121) of the patients (Table 2). We found 90 patients (25%) with one PIP, 27 (8%) with two PIP's, 2 (0,5%) with three PIP's and two (0,5%) with four PIP's. The most common PIP's identified by the STOPP criteria include (i) Drugs that predictably increase the risk of falls in older people: Benzodiazepines; (ii) Endocrine system: Sulphonylureas

with a long duration of action with type 2 diabetes mellitus; (iii) Analgesic Drugs:
Use of regular (as distinct from PRN) opioids without concomitant laxative; (iv)
Drugs that predictably increase the risk of falls in older people: Neuroleptic drugs
and (v) Analgesic drugs: Long-acting opioids without short-acting opioids for break-
through pain.

Table 2. Potentially inappropriate prescriptions as determined by STOPP criteria

Criterion	n
Indication of medication	
Any duplicate drug class prescription	4
Cardiovascular system	
Digoxin for heart failure with normal systolic ventricular function	1
Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	1
Loop diuretic for dependent ankle edema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure	5
Thiazide diuretic with current significant hypokalaemia, hypercalcaemia or with a history of gout	3
Antiplatelet/Anticoagulant Drugs	
Long-term aspirin at doses greater than 160mg per day	2
Aspirin with a past history of peptic ulcer disease without concomitant PPI	2
NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination	5
Central Nervous System and Psychotropic Drugs	
Tricyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	1
Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment	2
Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia	5
Antipsychotics in those with parkinsonism or Lewy Body Disease	1
Levodopa or dopamine agonists for benign essential tremor	5
First-generation antihistamines	5
Renal System	
Metformin if eGFR < 30	3
Gastrointestinal System	
PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	2
Respiratory System	
Theophylline as monotherapy for COPD	2
Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD	5
Musculoskeletal System	
NSAID with severe hypertension or severe heart failure	3
Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried	3
COX-2 selective NSAIDs with concurrent cardiovascular disease	3
Urogenital System	
Antimuscarinic drugs with dementia, or chronic cognitive impairment, narrow-angle glaucoma or chronic prostatism	4
Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope	1

Endocrine System	
Sulphonylureas with a long duration of action with type 2 diabetes mellitus	14
Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes	3
Drugs that predictably increase the risk of falls in older people	
Benzodiazepines	42
Neuroleptic drugs	8
Hypnotic Z-drugs	3
Analgesic Drugs	
Use of regular (as distinct from PRN) opioids without concomitant laxative	10
Long-acting opioids without short-acting opioids for break-through pain	6
Total	154

PPI = Proton-pump inhibitor; NSAID = Nonsteroidal anti-inflamatory drug; TCA = Tricyclic antidepressant; SSRI = Selective serotonin reuptake inhibitors; GFR = Glomerular filtration rate; COPD = Chronic obstructive pulmonary disease

Beers' criteria identified 104 PIP's (Table 3) distributed among 87 patients (25%). One PIP was described in 65 patients (19%), two PIP's in 21 patients (6%) and three PIP's in only one patient. The most common PIP's identified by Beers' criteria are (i) Benzodiazepines; (ii) Proton-pump inhibitors; (iii) Antipsychotics (first and second generation) and (iv) digoxin.

Table 3. Potentially inappropriate prescriptions described by Beers' criteria

Criterion	n
Independent of diagnosis	
Hydroxicine	4
Nitrofurantoin	2
Doxazosin	2
Digoxin	5
Amiodarone	1
Amitriptyline	3
Paroxetine	2
Benzodiazepines	42
Antipsychotics (first and second generation)	8
Zolpidem	3
Metoclopramide	4
Proton-pump inhibitors	11
Ibuprofen	3
Diclofenac	3
Considering diagnosis	
History of falls	
Benzodiazepines	2
Congnitive impairment	
Anticholinergics	4
Drug-drug interactions	
Warfarin – NSAIDs	3
Kidney malfunction	

Pregabalin eGFR<60	1
Tramadol eGFR<30	1
Ranitidine eGFR<50	1
Total	105

4.2. INTER-RATER AGREEMENT BETWEEN STOPP AND BEERS' CRITERIA

STOPP and Beers' criteria agree in the non-detection of any PIP in 218 patients (62%) and in the presence of PIP in 88 patients (25%). STOPP criteria detected more PIP which were not matched by Beers' criteria, 45 patients (15%) versus 14 patients (4%).

Table 4. Frecuency, percentage, Cohen's Kappa coefficient and Intraclass correlation coefficient of STOPP and Beers' criteria

STOPP/Beers	No PIM	Presence of PIM	Total
No PIM	218 (62%)	14 (4%)	232 (66%)
Presence of PIP	45 (13%)	74 (21%)	119 (34%)
Total	263 (75%)	88 (25%)	351

K = 0.60
ICC = 0.66

ICC = Intraclass correlation coefficient; K = Cohen's kappa coefficient

Cohen's Kappa coefficient (K) has a value of 0,60 which is in the border of moderate and good concordance. Intraclass correlation coefficient's (ICC) value is 0,63 indicating a good or substantial agreement.

4.3. ASSOCIATON BETWEEN POLYPHARMACY AND PIP

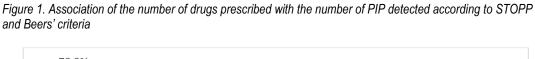The association between the number of prescribed chronic medications and the amount of PIP detected by both criteria show a growing trend (Table 5). An increase in the frequency of PIP's is seen when the number of drugs used increases from 1, 8% when applying STOPP criteria and 4% utilizing Beers' criteria to those in polypharmacy range that reach a 58% and 48% of PIP's for STOPP c Beers' criteria respectively.

Table 5. Number and % of PIP detected per patient according to STOPP and Beers' criteria

| Number of chronic drugs prescribed | Number (%) of PIP/patient | | | | | |
| | STOPP | | | Beers | | |
	0	1	2 or more	0	1	2 or more
1 or less	73 (92%)	6 (8%)	0 (0%)	76 (96%)	3 (4%)	0 (0%)
2 to 3	74 (71%)	27 (26%)	3 (3%)	84 (81%)	18 (17%)	2 (2%)
4 to 5	49 (56%)	29 (33%)	9 (11%)	62 (71%)	18 (21%)	7 (8%)
More than 6	34 (42%)	28 (35%)	19 (23%)	42 (52%)	26 (32%)	13 (16%)
Total	230 (65%)	90 (26%)	31 (9%)	264 (75%)	65 (19%)	22 (6%)

STOPP   Number of drugs – PIP Spearman's rho = 0.398; p < 0.001
Beers   Number of drugs – PIP Spearman's rho = 0.382; p < 0.001

Spearman's correlation coefficient for the number of medications and the amount of PIP is even in both classifications, for STOPP criteria it has a value of 0.398 and for Beers' criteria the value is 0.382, both being significant results (*** $p<0.001$) . This means a connection at the border between moderate and strong.

This increasing trend of PIP associated with the number of chronic drugs prescribed can be visualized in Fig. 1.

Figure 1. Association of the number of drugs prescribed with the number of PIP detected according to STOPP and Beers' criteria

5. DISCUSSION

Potentially inappropriate prescription is a serious problem that mainly affects the elderly. In our analysis a PIP rate of 34 and 25% according to STOPP and Beers' criteria respectively was detected among community-dwelling old adults. Other European studies show very similar data finding the range of detection of PIP according to STOPP between 35 and 42% and 25 to 28% for Beers' criteria [33,43]. In American literature these factors are even higher [44,45].

Concerns about the application of Beers' criteria to the European territory have been reinforced by this study [16, 46, 47]. Twenty seven percent of the drugs included in these criteria are not even commercialized in Spain, new active principles should also be added in order to improve their application [40]. Also, the designation of certain prescriptions might be inadequate, such as the prescription of amiodarone and doxazosin in older people regardless of the diagnosis [48]. Amiodarone may be the only effective agent for the control of arrhythmias and, even though it is not the first line of treatment, in particular cases its use is appropriate. Doxazosin is suitable in patients with resistant hypertension. In the present study, the three cases related to these prescriptions were justified.

Both criteria have a good degree of agreement, this has been reflected our results where 60% of the PIP detected by Beers could also be found by the STOPP criteria. This is mainly related to the detection of benzodiazepines and neuroleptics as potentially inappropriate prescription by both criteria. Both drugs represent a 48% of detected STOPP criteria and a 32% of Beer's criteria.

The high percentage of the PIP's detected related to benzodiazepines is a significant problem in Spain, where even the non-specialized literature has noticed. Its consumption is four times higher than other European countries, and it even exceeds the US consumption [49, 50]. In our study, according to STOPP they represent the 27% of all PIP's and for Beers' criteria a 40%. They have been described as inappropriate mainly due to their increased risk of falls and fractures and their contribution to mental deterioration [51, 52]. They have also been identified as the most common cause of potential problems in older people [53, 54, 55, 56] and their chronic use, which is more prevalent in females, has been described in more than

30% of women over 65. They represent an avoidable risk to the health of these patients and there are multiple pharmacological and non-pharmacological alternatives available to treat insomnia and anxiety [57], which are the main causes of their prescription.

The medical community is aware of the problem that benzodiazepines present in Spain however their prescription is prevalent, so we think that the true potential of these two tools is actually in the least prevalent criteria. Often these occur due to an error of the prescriber and/or because they are not known by the physician to be PIPs. Studies show that the contribution of a pharmacist can help to improve medication management in older patients and improve patient outcomes [58, 59, 60]. By simply applying these criteria most of the PIP's detected in this study would have been avoided easily.

Our results, like other previous studies [61,62] show that a higher number of chronic medications prescribed was associated with more inappropriate prescriptions reaching a prevalence of PIP around 50% according to both criteria. Polypharmacy is increasingly affecting older people and physicians justify it because of the complex comorbidity of these patients. A strong association has been described between polypharmacy and its negative clinical consequences in primary care [31, 63]. It is a health problem that leads to a greater number of adverse reactions and higher costs and therefore affects both the patient and the administration. Managing the patient's prescriptions in order to reduce the number of medications taken should be a priority in those patients using more than 6 drugs. This would reduce the number of potentially inappropriate medications significantly.

It is important to note that the lack of information in the medical records can be considered a limitation when applying the criteria, where some of the potentially inappropriate prescriptions may have been overestimated or underestimated. It should be kept in mind that the data have been collected and interpreted by a single person and that the detection of a PIP using these criteria cannot be considered a real problem until the clinical judgment of the prescriber is considered, according to the individual situation of each patient.

A practical solution for inappropriate prescribing has no yet been established, however the direction taken in recent years are improving the quality of the medication in elderly patients. Last year an IT tool called TRIM (Tool to Reduce Inappropriate Medications) was developed, it is based in an algorithm that uses both criteria analyzed in this study and it has shown promising results significantly reducing the amount of PIP [64, 65]. We believe that the future lies on this kind of approaches, creating a standard based on the existing literature including both of the criteria we have used here and others, such as the Taiwan criteria or the EU(7)PIM, and integrate it into a computer model. On top of this we think the contribution of the pharmacists is also needed since they are often in charge of alerting the physician to consider whether a medication is the possible cause of a negative result in the patient's health. Also they are in charge of programs that aim to reduce the amount of medication patients take.

6. CONCLUSION

The application of both the STOPP and Beers' criteria in our study has shown that we are facing a truly prevalent problem among the community-dwelling elderly patients. STOPP criteria detected a greater amount of PIP than Beer's criteria, however their agreement is consistent. In order to reduce the number of potentially inappropriate prescriptions physicians should reduce the number of polymedicated patients, which represent a large percentage of the PIP detected and develop standard computerized models that will help detect these inappropriate prescriptions in an automated way reducing the chance of errors.

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APPENDIX

APPENDIX A. SCREENING TOOL OF OLDER PERSONS' PRESCRIPTIONS (STOPP) VERSION 2.

TABLE A. STOPP CRITERIA

SECTION A. INDICATION OF MEDICATION

1. Any drug prescribed without an evidence-based clinical indication.

2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined.

3. Any duplicate drug class prescription e.g. Two concurrent NSAIDs, SSRIS, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).

SECTION B. CARDIOVASCULAR SYSTEM

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).

2. Verapamil or diltiazem with NYHA class iii or iv heart failure (may worsen heart failure).

3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).

4. Beta blocker with bradycardia (< 50/min), type ii heart block or complete heart block (risk of complete heart block, asystole).

5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem).

6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).

7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).

8. Thiazide diuretic with current significant hypokalaemia (i.e. Serum K+ < 3.0 mmol/l), hyponatraemia (i.e. Serum Na+ < 130 mmol/l) hypercalcaemia (i.e. Corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).

9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).

10. Centrally-acting antihypertensives (e.g. Methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).

11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.

12. Aldosterone antagonists (e.g. Spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum k should be monitored regularly, i.e. At least every 6 months).

13. Phosphodiesterase type-5 inhibitors (e.g. Sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. Systolic BP < 90 mmhg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse).

SECTION C. ANTIPLATELET/ANTICOAGULANT DRUGS

1. Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).

2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).

3. Aspirin, clopidogrel, dipyridamole, vitamin k antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. Uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).

4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).

5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin)

6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (no added benefit from dual therapy).

7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).

8. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. Thrombophilia) for > 6 months, (no proven added benefit).

9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. Thrombophilia) for > 12 months (no proven added benefit).

10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).
11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease).

SECTION D. CENTRAL NERVOUS SYSTEM AND PSYCHOTROPIC DRUGS

1. Tricyclic antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).

2. Initiation of Tricyclic antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).

3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).

4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. Serum Na+ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).

5. Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).

6. Antipsychotics (i.e. Other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms).

7. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity),

8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).

9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).

10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).

11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).

12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).

13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)

14. First-generation antihistamines (safer, less toxic antihistamines now widely available).

SECTION E. RENAL SYSTEM

1. Digoxin at a long-term dose greater than 125μg/day if eGFR < 30 ml/min/1.73m2 (risk of digoxin toxicity if plasma levels not measured).

2. Direct thrombin inhibitors (e.g. Dabigatran) if eGFR < 30 ml/min/1.73m2 (risk of bleeding).

3. Factor Xa inhibitors (e.g. Rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2 (risk of bleeding).

4. NSAID's if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function).

5. Colchicine if eGFR < 10 ml/min/1.73m2 (risk of colchicine toxicity).

6. Metformin if eGFR < 30 ml/min/1.73m2 (risk of lactic acidosis).

SECTION F. GASTROINTESTINAL SYSTEM

1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating parkinsonian symptoms).

2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).

3. Drugs likely to cause constipation (e.g. Antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).

4. Oral elemental iron doses greater than 200 mg daily (e.g. Ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day; no evidence of enhanced iron absorption above these doses).

SECTION G. RESPIRATORY SYSTEM

1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).

2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).

3. Anti-muscarinic bronchodilators (e.g. Ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).

4. Non-selective beta-blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm).

5. Benzodiazepines with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa (risk of exacerbation of respiratory failure).

SECTION H. MUSCULOSKELETAL SYSTEM

1. Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).

2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).

3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).

4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthrtitis (risk of systemic corticosteroid side-effects).

5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).

6. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. Allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).

7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).

8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease).

9. Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. Dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture).

SECTION I. UROGENITAL SYSTEM

1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).

2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).

SECTION J. ENDOCRINE SYSTEM

1. Sulphonylureas with a long duration of action (e.g. Glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).

2. Thiazolidenediones (e.g. Rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure).

3. Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).

4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).

5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).

6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).

SECTION K. DRUGS THAT PREDICTABLY INCREASE THE RISK OF FALLS IN OLDER PEOPLE

1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).

2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).

3. Vasodilator drugs (e.g. Alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers) with persistent postural hypotension i.e. Recurrent drop in systolic blood pressure ≥ 20mmhg (risk of syncope, falls).

4. Hypnotic Z-drugs e.g. Zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

SECTION L. ANALGESIC DRUGS

1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).

2. Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).

3. Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain).

SECTION N. ANTIMUSCARINIC/ANTICHOLINERGIC DRUG BURDEN

1. Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. Bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity).

APPENDIX B. 2015 AMERICAN GERIATRICS SOCIETY BEERS CRITERIA FOR POTENTIALLY INAPPROPRIATE MEDICATION USE IN OLDER ADULTS

TABLE B. BEERS' CRITERIA

TABLE B1. INDEPENDENT OF DIAGNOSIS

Anticholinergics

    <u>First-generation antihistamines</u>

        Brompheniramine

        Carbinoxamine

        Chlorpheniramine

        Clemastine

        Cyproheptadine

        Dexbrompheniramine

        Dexchlorpheniramine

        Dimenhydrinate

        Diphenhydramine (oral)

        Doxylamine

        Hydroxyzine

        Meclizine

        Promethazine

        Triprolidine

    <u>Antiparkinsonian agents</u>

        Benztropine (oral)

        Trihexyphenidyl

    <u>Antispasmodics</u>

        Atropine (excludes ophthalmic)

        Belladonna alkaloids

        Clidinium-chlordiazepoxide

        Dicyclomine

        Hyoscyamine

        Propantheline

        Scopolamine

Antithrombotics

    Dipyridamole, oral short-acting (does not apply to the extended release combination with aspirin)

    Ticlopidine

Anti-infective

    Nitrofurantoin

Cardiovascular

    <u>Peripheral alpha-1 blockers</u>

        Doxazosin

        Prazosin

        Terazosin

    <u>Central alpha blockers</u>

        Clonidine

        Guanabenz

        Guanfacine

        Methyldopa

Reserpine (>0.1 mg/d)

Disopyramide

Dronedarone

Digoxin

Nifedipine, immediate release

Amiodarone

Central nervous system

Antidepressants, alone or in combination

Amitriptyline

Amoxapine

Clomipramine

Desipramine

Doxepin >6 mg/d

Imipramine

Nortriptyline

Paroxetine

Protriptyline

Trimipramine

Antipsychotics, first- (conventional) and second- (atypical) generation

Barbiturates

Amobarbital

Butabarbital

Butalbital

Mephobarbital

Pentobarbital

Phenobarbital

Secobarbital

Benzodiazepines

Short- and intermediate- acting

Alprazolam

Estazolam

Lorazepam

Oxazepam

Temazepam

Triazolam

Long-acting

Clorazepate

Chlordiazepoxide (alone or in combination with amitriptyline or clidinium)

Clonazepam

Diazepam

Flurazepam

Quazepam

Meprobamate

Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics

Eszopiclone

Zolpidem

Zaleplon

Ergoloid mesylates (dehydrogenated ergot alkaloids) *isoxsuprine*

Endocrine

Androgens

   Methyltestosterone
   Testosterone
  Desiccated thyroid
  Estrogens with or without progestins
  Growth hormone
  Insulin, sliding scale
  Megestrol
  <u>Sulfonylureas, long-duration</u>
   Chlorpropamide
   Glyburide

Gastrointestinal
  Metoclopramide
  Mineral oil, given orally
  Proton-pump inhibitors

Pain medications
  Meperidine
  <u>Non-cyclooxygenase-selective</u>
   NSAIDs, oral:
   Aspirin >325 mg/d diclofenac
   Diflunisal
   Etodolac
   Fenoprofen
   Ibuprofen
   Ketoprofen
   Meclofenamate
   Mefenamic acid
   Meloxicam
   Nabumetone
   Naproxen
   Oxaprozin
   Piroxicam
   Sulindac
   Tolmetin
   Indomethacin
   Ketorolac, includes parenteral
  Pentazocine
  <u>Skeletal muscle relaxants</u>
   Carisoprodol
   Chlorzoxazone
   Cyclobenzaprine
   Metaxalone
   Methocarbamol
   Orphenadrine

Genitourinary
  Desmopressin

NSAID = nonsteroidal anti-inflammatory drug.

TABLE B2. CONSIDERING DIAGNOSIS

CARDIOVASCULAR

    Heart failure

        NSAIDs and COX-2 inhibitors

        Nondihydropyridine CCBs (diltiazem, verapamil) —avoid only for heart failure with reduced ejection fraction

        Thiazolidinediones (pioglitazone, rosiglitazone)

        Cilostazol

        Dronedarone (severe or recently decompensated heart failure)

    Syncope

        Acheis

        Peripheral alpha-1 blockers

            Doxazosin

            Prazosin

            Terazosin

        Tertiary TCAs

        Chlorpromazine

        Thioridazine

        Olanzapine

CENTRAL NERVOUS SYSTEM

    Chronic seizures or epilepsy

        Bupropion

        Chlorpromazine

        Clozapine

        Maprotiline

        Olanzapine

        Thioridazine

        Thiothixene

        Tramadol

    Delirium

        Anticholinergics (see table B5 for full list)

        Antipsychotics

            Benzodiazepines

            Chlorpromazine

        Corticosteroids

        H2-receptor antagonists

            Cimetidine

            Famotidine

            Nizatidine

            Ranitidine

        Meperidine

        Sedative hypnotics

    Dementia or cognitive impairment

        Anticholinergics (see table 7 for full list)

        Benzodiazepines

        H2-receptor antagonists

        Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics

            Eszopiclone

            Zolpidem

Zaleplon

<u>Antipsychotics</u>, chronic and as-needed use

History of falls or fractures

<u>Anticonvulsants</u>

<u>Antipsychotics</u>

<u>Benzodiazepines</u>

<u>Nonbenzodiazepine</u>, benzodiazepine receptor agonist hypnotics

Eszopiclone

Zaleplon

Zolpidem

<u>TCAs</u>

<u>SSRIs</u>

<u>Opioids</u>

Insomnia

<u>Oral decongestants</u>

Pseudoephedrine

Phenylephrine

<u>Stimulants</u>

Amphetamine

Armodafinil

Methylphenidate

Modafinil

<u>Theobromines</u>

Theophylline

Caffeine

Parkinson disease

<u>All antipsychotics</u> (except aripiprazole, quetiapine, clozapine)

<u>Antiemetics</u>

Metoclopramide

Prochlorperazine

Promethazine

<u>**GASTROINTESTINAL**</u>

History of gastric or duodenal ulcers

Aspirin (>325 mg/d)

Non-COX-2 selective NSAIDs

<u>**KIDNEY AND URINARY TRACT**</u>

Chronic kidney disease stages IV or less (creatinine clearance <30 ml/min)

NSAIDs (non-cox and cox-selective, oral and parenteral)

Urinary incontinence (all types) in women

Estrogen oral and transdermal (excludes intravaginal estrogen)

<u>Peripheral alpha-1 blockers</u>

Doxazosin

Prazosin

Terazosin

Lower urinary tract symptoms, benign prostatic hyperplasia

Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (table B5)

CCB = Calcium channel blocker; TCA = Tricyclic antidepressant; SSRI = Selective serotonin reuptake inhibitor.

TABLE B3. POTENTIALLY CLINICALLY IMPORTANT NON-ANTI-INFECTIVE DRUG–DRUG INTERACTIONS THAT SHOULD BE AVOIDED IN OLDER ADULTS

ACEIs	Amiloride or triamterene
Anticholinergic	Anticholinergic
Antidepressants (i.e., TCAs and SSRIs)	≥2 other CNS-active drugs[a]
Antipsychotics	≥2 other CNS-active drugs[a]
Benzodiazepines and nonbenzodiazepine, Benzodiazepine receptor agonist hypnotics	≥2 other CNS-active drugs[a]
Corticosteroids, oral or parenteral	NSAIDs
Lithium	ACEIs
Lithium	Loop diuretics
Opioid receptor agonist analgesics	≥2 other CNS-active drugs[a]
Peripheral Alpha-1 blockers	Loop diuretics
Theophylline	Cimetidine
Warfarin	Amiodarone
Warfarin	NSAIDs

[a] Central nervous system (CNS)-active drugs: antipsychotics; benzodiazepines; nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; tricyclic antidepressants (TCAs); selective serotonin reuptake inhibitors (SSRIs); and opioids.
ACEI = angiotensin-converting enzyme inhibitor.

TABLE B4. NON-ANTI-INFECTIVE MEDICATIONS THAT SHOULD BE AVOIDED OR HAVE THEIR DOSAGE REDUCED WITH VARYING LEVELS OF KIDNEY FUNCTION IN OLDER ADULTS

Cardiovascular or hemostasis	
Amiloride	<30
Apixaban	<25
Dabigatran	<30
Edoxaban	30–50
	<30 or >95
Enoxaparin	<30
Fondaparinux	<30
Rivaroxaban	30–50
	<30
Spironolactone	<30
Triamterene	<30
Central nervous system and analgesics	
Duloxetine	<30
Gabapentin	<60
Levetiracetam	≤80
Pregabalin	<60

Tramadol	<30
Gastrointestinal	
Cimetidine	<50
Famotidine	<50
Nizatidine	<50
Ranitidine	<50
Hyperuricemia	
Colchicine	<30
Probenecid	<30

TABLE B5. DRUGS WITH STRONG ANTICHOLINERGIC PROPERTIES

Antihistamines	**Antiparkinsonian agents**	**Skeletal muscle relaxants**
Brompheniramine	Benztropine	*Cyclobenzaprine*
Carbinoxamine	Trihexyphenidyl	*Orphenadrine*
Chlorpheniramine		
Clemastine		
Cyproheptadine		
Dexbrompheniramine		
Dexchlorpheniramine		
Dimenhydrinate		
Diphenhydramine		
(oral)		
Doxylamine		
Hydroxyzine		
Meclizine		
Triprolidine		
Antidepressants	**Antipsychotics**	**Antiarrhythmic**
Amitriptyline	Chlorpromazine	*Disopyramide*
Amoxapine	Clozapine	
Clomipramine	Loxapine	
Desipramine	Olanzapine	
Doxepin (>6 mg)	Perphenazine	
Imipramine	Thioridazine	
Nortriptyline	Trifluoperazine	
Paroxetine		
Protriptyline		
Trimipramine		
Antimuscarinics (urinary incontinence)	**Antispasmodics**	**Antiemetic**
Darifenacin	*Atropine (excludes ophthalmic)*	*Prochlorperazine*
Fesoterodine	*Belladonna*	*Promethazine*
Flavoxate	*alkaloids*	
Oxybutynin	*Clidiniumchlordiazepoxide*	
Solifenacin	*Dicyclomine*	
Tolterodine	*Homatropine*	
Trospium	*(excludes ophthalmic)*	
	Hyoscyamine	
	Propantheline	