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Mimica Matanović, Suzana; Vlahović-Palčevski, Vera

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REVIEW ARTICLE

Potentially inappropriate medications in the elderly: a comprehensive protocol

Suzana Mimica Matanović · Vera Vlahovic-Palcevski

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Abstract Elderly patients are at increased risk of drug-related morbidity and mortality. Avoiding the use of potentially inappropriate medications (PIMs) is one of the strategies that has been widely adopted to reduce the harmful consequences of drug use. There are several PIM screening tools available. In this review, we provide an overview of existing screening tools to detect PIMs in the elderly, emphasizing the advantages and disadvantages of each. Combining previously published and adopted tools (adjusted Beers list, French consensus panel, McLeod's list, and Lindblad's list of clinically important drug–disease interactions), we develop a new comprehensive tool that also includes the adjusted Hanlon's and Malone's lists of potentially serious drug–drug interactions in the elderly. In addition to listed PIMs and clinically important drug–drug interactions, alternative therapeutic solutions are suggested. The new protocol differentiates: drugs with an unfavorable benefit/risk ratio (to be avoided regardless of the underlying disease/condition), drugs with a questionable efficacy, and drugs to be avoided with certain diseases/conditions, and provides a list of potentially serious drug–drug interactions. A tool consisting of PIMs and potential drug–drug interactions within the same protocol provides more comprehensive quality assessment of drug-prescribing behavior to the elderly, which in turn may lead to better prescribing practices.

S. Mimica Matanović (✉)
Clinical Pharmacology Unit, University Hospital Center Osijek,
Osijek, Croatia
e-mail: mimica-matanovic.suzana@kbo.hr

S. Mimica Matanović
Department of Pharmacology, Medical School Osijek,
University J.J. Strossmayer Osijek,
Osijek, Croatia

V. Vlahovic-Palcevski
Clinical Pharmacology Unit, University Hospital Center Rijeka,
Rijeka, Croatia

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Introduction

The percentage of the total elderly population is increasing in most countries, and it is estimated that by 2050 almost 30% of the population in developed countries will be over 65 years of age [1]. Elderly patients consume approximately 30% of all healthcare resources and, therefore, the growth of this population group will have significant implications on future healthcare budgets [2]. Elderly individuals often have many chronic diseases and are consequently taking multiple medications. They also have increased risk for adverse drug reactions (ADRs) due to age-related changes in the pharmacodynamics and pharmacokinetics of drugs, co-morbidities, and polypharmacy [3]. It may thus be anticipated that this increase in the numbers of elderly people will also lead to higher drug-related morbidity and mortality [2, 4].

Suboptimal or inappropriate prescribing in elderly patients pose the risk of drug-related morbidity and mortality. Inappropriate prescribing includes the prescribing of medications with potentially serious drug–drug interactions or the underuse, overuse, and misuse of drugs. Misuse encompasses the use of potentially inappropriate medications (PIMs), inappropriate dose, or inappropriate duration of treatment. PIMs are defined as drugs with a potential risk that is higher than their potential benefit to the patient, particularly when safer alternative therapies exist for the same condition [4, 5].

Several screening tools for detecting PIMs in the elderly have been developed in the USA, Canada, and European countries [6–16]. Their role is to optimize the appropriateness of prescribing behavior and to reduce negative outcomes,

including preventable adverse drug effects (ADEs). These screening tools encompass lists of drugs that should generally be avoided by the elderly and drugs that should be avoided with certain diagnoses or conditions. While most of the protocols are explicit (criterion-based), there is only one implicit (judgement-based) protocol, the Medication Appropriateness Index (MAI), which was developed by Hanlon and colleagues [17] .

The aim of this review is to critically evaluate available protocols for detecting PIMs in the elderly and summarize these into a new comprehensive and widely applicable protocol.

Overview of the existing screening tools for detection of PIMs in the elderly

A literature search was performed within the MEDLINE, PubMed, OVID, and Google Scholar databases using MeSH terms "aged," "inappropriate prescribing," "clinical protocols," "medication errors," and "polypharmacy." Articles published between January 1991 and December 2010 were selected if they contained explicit criteria adressing potentially inappropriate prescribing in the elderly.

Table 1 summarizes the protocols and screening tools for detection of PIMs prescribed to the elderly, published in chronological order. For each tool in the table, data on the authors, year, country of origin, scope, main content, and main advantages/disadvantages are presented. One of the tools was developed by Barry et al. [13] to evaluate underprescribing, i.e., for detecting omission of evidence-based medications.

We considered the potential clinical applicability of the criteria and PIMs resulting in common clinical consequences as well as the wide applicability of a protocol to different healthcare settings and different geographical regions to be advantageous. Limitations or disadvantages of a protocol were considered to be a lack of clinical assessment and evaluation or validation of the protocol, incomplete drug listings, and/or obsolete drugs listed.

According to different authors, newer criteria offer certain innovations and improvements compared to those on the original Beers list and address drug–drug interactions, underuse of drugs, drugs with questionable efficacy, among others [18–20]. However, while several new tools need to be evaluated and assessed in clinical studies, Beers criteria have been the most widely used and an association of the listed drugs with adverse outcomes has been shown by number of authors [21–34].

The new comprehensive protocol

Taking into account the reported advantages and disadvantages of existing screening tools, it may be assumed that by combining their clinically most useful parts together, it should be possible to develop a new comprehensive tool. In evaluating the advantages of previous tools, we focused on the potential clinical applicability of the criteria and on PIMs having common clinical consequences in the elderly [e.g., focusing on non-steroid anti-inflammatory drugs (NSAIDs), associated with multiple possible adverse outcomes].

The new protocol is developed by combining the adjusted Beers list, the French consensus panel, McLeod's list, and Lindblad's list of clinically important drug–disease interactions, with the addition of several new drugs [8, 10–12]. As part of the protocol, a list of clinically important drug–drug interactions in the elderly is developed by modifying Malone's and Hanlon's lists and adding four new drug–drug interactions [35, 36]. A clinically based approach was used to build the protocol. The new criteria have been shown by many researchers to be associated with adverse clinical and healthcare outcomes, thus confirming their relevance [27–34]. By combining parts of the North American and European tools together, we assume that new combined tool will be widely applicable in the elderly population (defined as 65 years or older).

The protocol groups PIMs into: (1) those with an unfavorable benefit/risk ratio (drugs to be avoided regardless of the underlying disease/condition); (2) drugs with a questionable efficacy, and (3) drugs to be avoided with certain diseases/conditions. Those three major subgroups are defined similarly in the French consensus panel and on Beers list. For each criterion listed, a possible alternative solution is given [8, 12, 16]. Part (4) of the protocol presents the list of potentially serious drug–drug interactions in the elderly population.

Drugs with unfavorable benefit/risk ratio (part 1 of new protocol)

The list of drugs with an unfavorable benefit/risk ratio is based on a combination of the adjusted Beers list and the French consensus panel, as shown in Table 2, and consists of 33 criteria or individual drugs [10, 12]. Drugs defined solely by the French panel include antipsychotic drugs with anticholinergic properties and concomitant use of ≥2 NSAIDs, clonidine, and moxonidine among the centrally acting antihypertensives and dipyridamole (according to Beers list, dipyridamole is inappropriate medication only in patients receiving anticoagulant therapy or in those with blood clotting disorders). These drugs are included in the new protocol because their use can lead to severe ADRs [37–42] .

Drugs defined solely by the Beers list include: doxazosin, amiodarone, fluoxetine, thioridazine, ferrous sulfate >325 mg/day, estrogens only (oral), methyltestosterone, long-term use

Table 1 Characteristics of existing screening tools for potentially inappropriate medications

Authors	Year	Country	Scope	Main content	Pro's and con's
Beers et al. [6]	1991	USA	Nursing home residents ≥65 years	Delphi consensus based. Thirty criteria for drugs to be avoided in the elderly	Pros: the first tool developed for PIM screening in the elderly Cons: many drugs from the list are unavailable in other countries. Developed for nursing home residents but also used in studies with other patient populations
Beers [7]	1997	USA	All patients ≥65 years	Delphi consensus based; updated and expanded version. Fifteen drugs omitted from the original version. Contains 28 drugs or drug classes to be avoided in ambulatory elderly independent of diagnosis and 35 drugs or drug classes to be avoided in patients with certain disease or condition	Pros: more generally applicable (for ambulatory patients) Cons: many drugs from the list are unavailable in other countries. Drug–drug interactions and duplication of treatments are not evaluated
McLeod et al. [8]	1997	Canada	All patients ≥65 years	Delphi consensus based. Thirty-eight inappropriate practices (grouped into cardiovascular, psychotropic, analgesic and miscellaneous drugs) • drug generally contraindicated (18) • drug–disease interactions (16)• drug–drugs interactions (4)	Pros: Nine inappropriate practices address prescribing of NSAIDs, including long-term prescription in patients with a history of pepticulcer, hypertension, chronic renal, or congestive heart failure. Drug–drug interactions addressed. Alternative therapy for each criterion suggested Cons: some of the criteria obsolete (e.g., beta blockers in patients with asthma or COPD or beta blockers in patients with congestive heart failure)
Naughler et al. [9]	2000	Canada	All patients ≥70 years	Derived from McLeod's list. Fourteen inappropriate combinations of drugs and diseases	Pros: simple and easily applicable tool Cons: some of the criteria obsolete (e.g., beta blockers in patients with asthma or COPD or beta blockers in patients with congestive heart failure). Three of the criteria involve today uncommonly used tricyclic antidepressants
Fick et al. [10]	2003	USA	All patients ≥65 years	Delphi consensus based updated version of Beers list. Sixty-eight criteria: 48 drugs or drug classes generally to be avoided; 20 diseases or conditions with drugs to be avoided	Pros: the most widely cited explicit criteria. Association with adverse healthcare outcomes shown Cons: many drugs from the list are unavailable in other countries. Drug–drug interactions and duplication of treatments are not evaluated. Appropriateness of some drugs from the list still subject of debate (e.g., amiodarone or amitriptyline). Only four inappropriate practices associated with the use of NSAIDs addressed
Lindblad et al. [11]	2006	USA	All patients ≥65 years	Delphi consensus based. Twenty-eight clinically important drug–disease interactions, involving 14 diseases or conditions. Eleven drug-disease interactions included on Beers list and 5 included in McLeod's list	Pros: simple and easily applicable tool. Introduces new criteria not defined by Beers' or McLeod's list Cons: drugs to be avoided regardless of a disease or condition are not included
Laroche et al. [12]	2007	France	All patients ≥75 years	Delphi consensus based, first European screening tool. Thirty-four criteria for inappropriateness. PIMs grouped into those with unfavorable benefit/risk ratio (25 criteria), questionable efficacy (one criterion), and both unfavorable benefit/risk ratio and questionable efficacy	Pros: Alternative drugs or therapeutic abstention for each criterion suggested. The first tool to address drugs with questionable efficacy as potentially

Table 1 (continued)

Authors	Year	Country	Scope	Main content	Pro's and con's
				(7 criteria). Twenty-nine criteria are independent of a disease or condition and five are linked to disease or condition	inappropriate (cerebral vasodilators). Duplication of treatments addressed as potentially inappropriate Cons: underuse of drugs is not addressed. Needs to be assessed and confirmed in clinical studies
Barry et al. [13]	2007	Ireland	All patients ≥65 years	Delphi consensus based. START (Screening Tool to Alert Doctors to Right Treatment). Twenty-two medications included. Underprescribing or omission of clinically indicated, evidence-based medications evaluated (e.g., ACE inhibitors in chronic heart failure or beta blocker in chronic stable angina, if no contraindications).	Pros: first tool evaluating underuse of drugs
Gallagher et al. [14]	2008	Ireland	All patients ≥65 years	Delphi consensus based. STOPP (Screening Tool of Older Persons' Prescription). Sixty-five criteria for PIMs evaluation arranged according to relevant physiological systems.	Pros: innovative approach introduced (first tool to address inappropriate use of PPI for peptic ulcer and use of aspirin without history of coronary, cerebral or peripheral vascular symptoms or occlusive event). Seven criteria address prescribing of NSAIDs, including prescription in patients hypertension, chronic renal or congestive heart failure. Drug class duplication and drug–drug interactions addressed as potentially inappropriate. Sensitive for identifying patients with potential to suffer PIMs-related ADRs Cons: drugs with questionable efficacy not addressed. Needs to be assessed and confirmed in clinical studies.
Rognstad et al. [15]	2009	Norway	Patients ≥70 years in general practice	Delphi consensus based. Twenty-one explicit criteria for single drugs and 15 criteria for drug–drug interactions.	Pros: Lists inappropriate single drugs (i.e., theophylline or sotalol) and drug combinations [e.g., combination of NSAIDs (or coxib) and ACE inhibitors (or ARBs) which may increase the risk of renal failure, or combination of NSAIDs and diuretics, resulting in reduced diuretic effect] not addressed by previous tools Cons: aimed at patients in general practice. Needs to be assessed and confirmed in clinical studies
Holt et al. [16]	2010	Germany	All patients ≥65 years	Delphi consensus based. Lists a total of 83 drugs to be avoided regardless of the underlying disease/condition, contained in 18 drug classes.	Pros : easily applicable tool. Names main concerns, possible therapeutic alternatives and precautions to be taken. Lists many drugs not addressed by previous tools (e.g., ketoprofen, meloxicam, prasugrel, flecainide, metildigoxin, haloperidol >2 mg, zaleplon >5 mg, phenobarbital). Drugs with questionable efficacy are addressed (circulation-promoting agents) Cons: aimed primarily at German elderly population. Needs to be assessed and confirmed in clinical studies

ACE, Angiotensin converting enzyme; ADRs, adverse drug reactions; ARBs, angiotensin II receptor blockers; COPD, obstructive pulmonary disease; NSAIDs, non-steroid anti-inflammatory drugs; PIMS, potentially inappropriate medications, PPI, proton pump inhibitor

Table 2 Drugs with unfavorable benefit/risk ratio

Drug	Possible adverse effects	Possible therapeutic solutions
Analgesics		
Indomethacin	Severe CNS side effects	Short-term use of a weak NSAID (e.g., ibuprofen) or acetaminophen or a weak opioid (e.g., tramadol)
Concomitant use of 2 or more NSAIDs	No enhancement of efficacy, increased risk of ADRs	Short-term use of only one weak NSAID (e.g., ibuprofen)
Long-term use of full-dosage, longer half-life NSAIDs: naproxen, piroxicam	Increased risk of GI bleeding, renal failure, high blood pressure and heart failure	Short-term use of a weak NSAID (e.g., ibuprofen) or use of acetaminophen or a weak opioid (tramadol, codeine)
Drugs with anticholinergic properties		
Antidepressants: amitriptyline, maprotiline	Muscarinic-blocking side-effects, cardiotoxicity when overdosed	SSRIs (except flouxetine) or SNRIs
Antipsychotic drugs: fluphenazine, levomepromazine	Muscarinic-blocking side-effects	Atypical antipsychotic drug with less anticholinergic activity (e.g., olanzapine, risperidone, quetiapine)
Antihistamines: diphenhydramine, dimenhydrinate	Muscarinic-blocking side-effects, sedation, drowsiness	Antihistamines without anticholinergic activity (e.g., cetirizine, levocetirizine, loratadine, desloratadine)
Concomitant use of drugs with anticholinergic properties	Enhanced anticholinergic ADRs	Avoid drugs with anticholinergic activity in general
Sedative or hypnotic drugs		
Long-acting benzodiazepines: diazepam, bromazepam, nitrazepam, flurazepam	Prolonged sedation and drowsiness, increased risk of falls	Short-acting benzodiazepines given in dose ≤half the dose in younger adults
Short-acting benzodiazepines, dose >half the dose in younger adults (lorazepam >3 mg, oksazepam >60 mg, alprazolam >2 mg)	Increased risk of ADRs without increased efficacy	Short-acting benzodiazepines given in dose ≤half the dose in younger adults
Meprobamat	Very sedative properties, addictive with prolonged use	Short-acting benzodiazepines given in dose ≤half the dose in younger adults
Antihypertensives		
Methyldopa	Bradycardia, exacerbation of depression	Other antihypertensive drugs, except the ones listed here [i.e., diuretics, calcium channel blockers (except short-acting ones), ACE inhibitors, AT1 blockers]
Clonidine	Ortostatic hypotension	
Moxonidine	Headache, vertigo, asthenia	
Nifedipine, short-acting	Postural hypotension, myocardial infarction, stroke	
Doxazosine	Hypotension, dry mouth, urinary incontinence	
Anti-arrhythmics		
Amiodarone	Prolonged QT interval, risk of "torsade de pointes", reduced efficacy in the elderly	Other antiarrhythmics, depending on the type of arrhythmia (e.g., propafenone, beta blockers, calcium channel blockers)
Disopiramide	Negative inotropic and anticholinergic properties	
Digoxin >0.125 mg	Reduced renal clearance and increased risk of ADRs	Digoxin <0.125 mg, with serum concentrations 0.5–1.2 ng/ml
Antiplatelet drugs and vasodilators		
Ticlopidine	Blood and liver adverse effect	Clopidogrel, aspirin
Dipiridamole	Vasodilation and postural hypotension, questionable efficacy	
Drugs used to treat gastrointestinal disorders		
Cimetidine	CNS adverse events, confusion, common drug interactions	Other H_2-antagonists or PPIs
Scopolamine	Muscarinic-blocking agent, no proven efficacy	Mebeverine
Long-term use of stimulant laxatives: bisacodyl, sennosides	Worsening of irritable bowel syndrome	Osmotic laxatives (e.g., lactulose)

Table 2 (continued)

Drug	Possible adverse effects	Possible therapeutic solutions
Long-acting sulfonylureas		
Chlorpropamide, glibenclamide	Protracted hypoglycemia	Short- or immediate-acting sulfonylureas (e.g., glipizide, gliclazide)
Muscle relaxants		
Baclofen	Drowsiness, amnesia, fall	Thiocolchicoside, mephenesine
Opioid analgesics		
Pentazocin	More CNS adverse effects, including confusion and hallucinations; mixed agonist and antagonist	Other opioids, with more favorable risk/benefit profile (e.g., tramadol, oxycodone)
Meperidine	Not an effective oral analgesic in doses commonly used. May cause confusion	
Other		
Ferrous sulfate >325 mg/day	Increased incidence of constipation	Dose <325 mg/day
Nitrofurantoin	Can induce renal insufficiency, pneumopathy, peripheral neuropathy, allergic reaction	Other type of antibiotics, depending on microbiology results
Methyltestosterone	Potential for prostatic hypertrophy and cardiac problems	Avoid testosterone substitution
Estrogens only (oral)	Carcinogenic potential and lack of cardioprotective effect	If indicated, use combination of estrogens with progesterones. HRT to be used for the shortest time possible.
Thioridazine	Greater potential for CNS and extrapyramidal adverse effects	Atypical antipsychotic drug with less extrapyramidal adverse effects (e.g., olanzapine, quetiapine)
Daily fluoxetine	Long half-life of drug and risk of producing excessive CNS stimulation, sleep disturbances, and increasing agitation	Other SSRIs or SNRIs

CNS, Central nervous system; GI, gastrointestinal; , SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors

of naproxen and piroxicam, and use of the opiates pentazocine and meperidine. French experts did not find those drugs relevant. However, since these drugs are commonly used and possible ADRs might have serious consequences, they are included the new protocol [43–49]. For example, even though the European Medicines Agency in 2007 recommended restricted use of piroxicam, it seems that the extent of its restricted prescribing among the elderly is not satisfactory [50–52]. Amiodarone is a commonly prescribed antiarrhythmic drug, partly due to the lack of similar antiarrhythmic drugs on the market. However, not only is it associated with QT prolongation in the elderly, but its complex pharmacokinetic properties, very long half-life, and possible multiple drug interactions make it a drug that warrants high caution when used [45–49].

Drugs with unfavorable benefit/risk ratio listed in the new protocol that are on neither the French or Beerslist include glibenclamide, a long-acting sulphonylurea drug associated with a higher risk of inducing prolongedhypoglycemia, and promazine, an antipsychotic drug with strong anticholinergic properties [40, 53, 54].

The remaining drugs with an unfavorable benefit/risk ratio on the new list are in agreement with both the French and Beers list as being potentially inappropriate.

Drugs with a questionable efficacy (part 2 of new protocol)

The French list of PIMs in the elderly is the only available tool that contains drugs with questionable efficacy as potentially inappropriate [12]. Medications defined as questionably efficacious are cerebral vasodilators, such as gingko biloba, pentoxyphylline, piracetam, and dihydroergotoxine. These four commonly used vasodilator drugs are included in the new protocol, with the addition of two more drugs, betahistine and cinarizine (except in the indication of Meniere syndrome and vestibular vertigo), which are often used as cerebral vasodilators in patients with cerebrovascular insufficiency (Table 3). Drugs used as cerebral vasodilators do not have a proven efficacy but they do have a potential to cause ADRs in the elderly, such as postural hypotension, falls, headache, or stomach upset [55–60].

The French panel recognizes a category of drugs with both unfavorable benefit/risk ratio and questionable efficacy, such as nitrofurantoin, anticholinergic antispasmodic scopolamine, or short/intermediate half-life benzodiazepines in doses higher than half the dose given in the young patients. In the new protocol these drugs are classified among those with unfavorable benefit/risk ratio [12].

Drugs to be avoided with certain diseases/conditions (part 3 of new protocol)

This part of the new protocol includes 71 individual drug–disease interactions involving 28 diseases or conditions, as shown in Table 4. Criteria from the adjusted Beers list, McLeod's list, and Lindblad's list of clinically important drug–disease interactions are combined and respective data updated [10–12, 61–69]. Some of the inappropriate drug–disease combinations are defined by all three tools, such as NSAIDs in peptic ulcer disease or tricyclic antidepressant in benign prostate hyperplasia. However, only McLeod's list recognizes the long-term use of NSAIDs in patients with heart failure and hypertension or long-term use of NSAIDs to treat osteoarthritis regardless of the accompanying disease, as potentially inappropriate. NSAIDs are commonly prescribed to the elderly, and their risk/benefit ratio should regularly be checked in individual patients. As a general principle, the long-term use of NSAIDs should be avoided in patients with chronic renal or heart failure, hypertension, and peptic ulcer disease, but also in older patients regardless of their underlying disease [38]. Not only is there always the possibility that NSAIDs can worsen renal or heart failure or cause gastrointestinal toxicity, but there are emerging data on the increased risk of stroke and myocardial infarction associated with their use [39]. Also, gastrointestinal bleeding is often the most common cause of ADRs related hospital admissions in the elderly [70–72]. Therefore, it seems reasonable to include McLeod's NSAIDs criteria in the new

Table 3 Drugs with questionable efficacy

Drug	Possible adverse effects	Possible therapeutic solutions
Cerebral vasodilators		
Dihydroergotoxine Gingko biloba Pentoxifylline Piracetam Betahistine (except in the indication of Meniere syndrome and vestibular vertigo) Cinarizine (except in the indication of Meniere syndrome and vestibular vertigo)	No really proven efficacy while there is risk of postural hypotension, falls, headache, or stomach upset	Therapeutic abstention

Table 4 Drugs to be avoided with certain diseases/conditions

Disease or condition/drug	Possible adverse effects	Possible therapeutic solutions
Heart failure		
Disopyramide	Negative inotropic effect	Antiarrhythmic drug without negative inotropic effect
High sodium content drugs (sodium and sodium salts [bicarbonate, biphosphate, citrate, phosphate, salicylate, and sulfate])	Potential to promote fluid retention and exacerbation of heart failure	Avoid this type of drugs
Calcium-channel blockers, except , dihydropyridines	Negative inotropic effect.	Avoid verapamil and dilatiazem in these patients. Depending on the underlying diagnosis (hypertension, angina), drug without negative inotropic effect should be used
Long-term prescription of NSAIDs	Potential to promote fluid retention and exacerbation of heart failure	Acetaminophen or a weak opioid (e.g., tramadol). Monitoring of cardiovascular function.
Hypertension		
Pseudoephedrine	May produce elevation of blood pressure secondary to sympathomimetic activity	Avoid over-the-counter cold and cough medications containing this substance.
Long-term prescription of NSAIDs	May produce elevation of blood pressure secondary to salt and water retention	Acetaminophen or a weak opioid (e.g., tramadol). Monitoring blood pressure.
Chronic renal failure		
Long-term prescription of NSAIDs	May reduce renal blood flow and worsen renal failure	Acetaminophen or a weak opioid (e.g., tramadol). Monitoring renal function.
Gastric or duodenal ulcers		
NSAIDs	May exacerbate existing or produce new ulcers	Acetataminophen or a weak opioid (e.g., tramadol). If use of NSAID is deemed unavoidable, use NSAID with less gastrointestinal risk (e.g., ibuprofen) in combination with proton pump inhibitors.
Aspirin	May exacerbate existing or produce new ulcers	Use in combination with proton pump inhibitors
Seizures or epilepsy		
Clozapine, thioridazine	May lower seizure threshold	Atypical antipsychotic drug without proconvulsive effect and with a favorable risk to benefit profile (e.g., olanzapine, risperidone, quetiapine)
Bupropion	May lower seizure threshold	SSRI (except fluoxetine) or SSNI
Blood clotting disorders or receiving anticoagulant therapy		
NSAIDs	Increased potential for bleeding	For analgesia use acetaminophen or a weak opioid (e.g., tramadol)
Aspirin Clopidogrel	Increased potential for bleeding	If the combination is deemed unavoidable, use with extreme caution and regular monitoring of the patient
Cimetidine (those taking warfarin)	May elevate INR values and increase potential for bleeding	Other H_2-antagonist or proton pump inhibitor
Bladder outflow obstruction		
Anticholinergics	May decrease urinary flow, leading to urinary retention	Use drugs without anticholinergic activity
Stress incontinence		

Table 4 (continued)

Disease or condition/drug	Possible adverse effects	Possible therapeutic solutions
Alpha blockers (doxazosin, urapidil) Anticholinergics Tricyclic antidepressants Long-acting benzodiazepines	May induce or worsen incontinence	Use alternative antihypertensives (e.g., ACE inhibitors or AT1 blockers), antidepressants (SSRI or SNRI) and sedative/hypnotics (e.g., short-term use of short-acting benzodiazepines). Avoid anticholinergics.
Arrhythmias		
Tricyclic antidepressants	Concern due to proarrhythmic effects and ability to produce QT interval changes	SSRI (except fluoxetine) or SSNI
AV block		
Tricyclic antidepressants	May worsen heart block	SSRI (except fluoxetine) or SSNI
Digoxine Verapamil	May worsen heart block	Avoid digoxine, non-dihydropyridine calcium channel blockers, beta blockers and antiarrhythmics
Insomnia		
Decongestants	Concern due to CNS stimulant effects	Short term topical application
Theophylline		Inhaled brochodilators
Methylphenidate		Avoid this type of drug
MAO inhibitors		Another type of antidepressant
Parkinson disease		
Metoclopramide	Concern due to their antidopaminergic/cholinergic effects	Another antiemetic drug
Conventional antipsychotics (fluphenazine, haloperidol)		Atypical antipsychotics with less D2-blocking activity (e.g., quetiapine or clozapine)
Acetylcholinesterase inhibitors (donepezil)		Memantine for treatment of dementia
Depression		
Long-term benzodiazepine use	May produce or exacerbate depression	Short-term benzodiazepine use
Methylphenidate		Avoid this type of drug
Sympatholytic agents: methyldopa and reserpin		Another type of antihypertensive drugs (including beta blockers)
Anorexia and malnutrition		
CNS stimulants (methylphenidate)	Concern due to appetite-suppressing effects	Avoid this type of drugs
Fluoxetine		Use cautiously another type of SSRI or SNRI with shorter half-life
Syncope or falls		
Short- to intermediate-acting benzodiazepines	May produce ataxia, impaired psychomotor function, syncope, and additional falls	Avoid benzodiazepines
Long-acting benzodiazepines		Avoid benzodiazepines
Tricyclic antidepressants		SSRI (except fluoxetine) and SRNI
Conventional antipsychotics (fluphenazine, haloperidol)		Atypical antipsychotics with less alpha blocking activity (e.g., quetiapine, ziprasidone, aripiprazole)

Table 4 (continued)

Disease or condition/drug	Possible adverse effects	Possible therapeutic solutions
SIADH/hyponatremia		
SSRIs	May exacerbate or cause SIADH	Most antidepressants and antipsychotics linked to SIADH. Consider stopping the treatment or use a drug with a different pharmacological profile and monitor serum sodium levels. Consider concomitant treatment with demeclocycline
Obesity		
Olanzapine	May stimulate appetite and increase weight gain	Atypical antipsychotic drug with less effect on weight gain (e.g., ziprasidone or aripiprazole)
COPD or asthma		
Long-acting benzodiazepines	May exacerbate or cause respiratory depression	Short-term use of short-acting benzodiazepines
Beta blockers—nonselective		Cardioselective beta-blockers
Chronic constipation		
Calcium channel blockers	May cause constipation	Other types of antihypertensives, except centrally acting, or another types of antianginal drugs (e.g., beta blockers, nitrate)
Anticholinergics		Avoid anticholinergics.
Centrally acting antihypertensives		Other types of antihypertensives, except calcium channel blockers
Opioid analgesics		Concomitant use of osmotic laxatives
Gout		
Thiazide diuretics	May precipitate or worsen gout	Use different type of antihypertensive (e.g., AT1 blocker losartan or a calcium channel blocker amlodipine)
Diabetes		
Corticosteroids	May precipitate or worsen diabetes	If corticosteroid therapy is unavoidable, use smallest dose possible and monitor blood glucose
Narrow-angle glaucoma		
Anticholinergics	Acute-angle glaucoma risk increased	Use drugs without anticholinergic activity
Osteoarthritis		
Long-term prescription of NSAIDs	May cause gastropathy, bleeding and salt and water retention	Acetaminophen or a weak opioid (e.g., tramadol). NSAIDs to be used for the shortest time possible (considering gastrointestinal risk of an individual NSAIDs)
Extrapyramidal effects of antipsychotic drugs		
Anticholinergics (e.g., biperiden)	May cause agitation, delirium and impaired cognition	Atypical antipsychotic drug with less extrapyramidal adverse effects (e.g., olanzapine, quetiapine)
Dementia		
Anticholinergics	May worsen cognitive impairment	Avoid all anticholinergics
Biperiden		Avoid and use other antiparkinson drug

Table 4 (continued)

Disease or condition/drug	Possible adverse effects	Possible therapeutic solutions
All benzodiapines		Short-term use of low-dose benzodiazepines
Barbiturates		Avoid this type of drugs
Conventional neuroleptics		Atypical antipsychotics: risperidone, olanzapine, aripiprazole
Postural hypotension		
Thioridazine	May worsen postural hypotension	Atypical antipsychotic drug without alpha blocking properties (e.g., olanzapine, risperidone, quetiapine)
Tricyclic antidepressants		SSRI (except fluoxetine) or SSNI
Raynaud disease or peripheral vascular disease		
Long-term prescription of beta blockers	May worsen the underlying condition	Calcium channel blocker

AV, Atrioventricular; INR, international normalized ratio; MAO inhibitors, monoamine oxidase inhibitors; SIADH, syndrome of inappropriate antidiuretic hormone hypersecretion

PIMs screening tool. Preventing excessive NSAID use in the elderly is one of the most important strategies to reduce drug-related morbidity and mortality.

Lindblad's list defines corticosteroid use in diabetic patients or opiate use in patients with constipation as inappropriate [11]. Both of these drug–disease combinations are considered clinically important and included in the new protocol.

Potentially serious drug–drug interactions (part 4 of new protocol)

In the quality assessment of drug-prescribing behavior to the elderly, an evaluation of potential drug–drug interactions leading to clinically important events is necessary. A list of 25 Delphi method-based drug–drug interactions with the greatest clinical importance in the general population was developed by Malone and colleagues in 2004 [35]. It was an important expert-based attempt to assess the clinical importance of drug interactions. These 25 interactions mostly involve drugs with a narrow therapeutic index (i.e., warfarin, cyclosporine, or digoxin) and generally are pharmacokinetic in their origin, acting through inhibition or induction of hepatic drug metabolism. Hanlon and Schmader [36] analyzed possible drug interactions in the elderly and suggested broadening Malone's list with seven clinically significant pharmacokinetic drug–drug interactions involving antiarrythmics, 12 involving antiepileptics, and 15 involving other drugs. They also suggested adding nine clinically significant pharmacodynamic drug–drug interactions, such as the combination of ACE inhibitors with potassium-sparing diuretics or potassium supplements [36].

In order to extend the evaluation of prescribing quality, we included the adjusted Malone's and Hanlon's lists of potentially serious drug–drug interactions in the new screening tool (Table 5) [35, 36]. As Malone's list focuses on the general population, we excluded drugs never or rarely prescribed in the elderly (e.g, oral contraceptives, zidovudine, or dexfenfluramine). Sibutramine was also excluded as it was withdrawn from all markets in the European Union in January 2010 due to increased cardiovascular risk [73]. The original Malone's list (25 drug–drug interactions) was reduced to 17 drug interactions overall. Among other potential clinically important drug combinations assessed by the Malone's expert panel but not reaching the final list were four combinations of drugs commonly used by the elderly: levodopa–monoamine oxidase inhibitors inhibitors; potassium–potassium-sparing diuretics; HMG Co-A reductase inhibitors–gemfibrozil; cytochrome P450 (CYP) 3A4-metabolized HMG Co-A reductase inhibitors–macrolide antibiotics [35]. In addition to these four combinations, the new protocol includes another four important potential interactions of drugs commonly prescribed to the elderly and

Table 5 Potentially serious drug–drug interactions

1. Clinically significant pharmacokinetic drug-drug interactions[a]

Antiarrhythmics

- Disopyramide–Cimetidine ↑
- Disopyramide–Macrolides (except azithromycin) ↑
- Procainamide–Amiodarone ↑
- Procainamide–Cimetidine ↑
- Procainamide–Trimethoprim ↑
- Quinidine–Cimetidine ↑
- Quinidine–Fluvoxamine ↑

Antiepileptics

- Carbamazepine–Danazol ↑
- Carbamazepine–Diltiazem ↑
- Carbamazepine–Macrolides ↑
- Carbamazepine–Verapamil ↑
- Phenytoin–Amiodarone ↑
- Phenytoin–Cimetidine ↑
- Phenytoin–Fluoxetine ↑
- Phenytoin–Isoniazid ↑
- Phenytoin–Omeprazole ↑
- Quinidine–Phenytoin ↓
- Theophylline–Phenytoin ↓
- Warfarin Phenytoin–PT-INR ↓

Other drugs with low therapeutic index

- Digoxin–Clarithromycin ↑
- Digoxin–Amiodarone ↑
- Digoxin–Propafenone ↑
- Digoxin–Quinidine ↑
- Digoxin–Verapamil ↑
- Lithium–ACE inhibitors ↑
- Lithium–Diuretics ↑
- Lithium–NSAIDs ↑
- Procainamide–Cimetidine ↑
- Salicylates–Probenecid ↑
- Theophylline–Cimetidine ↑
- Theophylline–Erythromycin, clarithromycin ↑
- Warfarin–Amiodarone ↑
- Warfarin–Macrolides ↑
- Warfarin–Quinolones ↑
- Warfarin–Sulfamethoxazole ↑

2. Drug–drug interactions selected by Malone et al. as having greatest clinical importance (pharmacokinetic and pharmacodynamic)[b]

Benzodiazepines–Azole antifungal agents

Cyclosporine–Rifampin

Ergot alkaloids–Macrolide antibiotics (except azithromycin)

MAO inhibitors–Sympathomimetics (dopamine, ephedrine, phenylephrine, pseudoephedrine)

Meperidine–MAO inhibitors

Methotrexate–Trimethoprim

Nitrates–Sildenafil

SSRIs–MAO inhibitors

Theophyllines–Fluvoxamine

Theophyllines–Quinolones

Thiopurines–Allopurinol
Warfarin–Fibric acid derivatives
Warfarin–NSAIDs
Warfarin–Cimetidine
Warfarin–Thyroid hormones
Warfarin– Barbiturates
3. Other clinically important drug–drug interactions (pharmacokinetic and pharmacodynamic)[c]
Atorvastatin/simvastatin–Amiodarone
Potassium– Potassium-sparing diuretics
Clopidogrel–PPIs
Levodopa–MAO inhibitors
SSRIs–Metoclopramide
SSRIs–Tramadol
HMG Co-A reductase inhibitors–gemfibrozil
Atorvastatin/simvastatinMmacrolide antibiotics
4. Clinically significant pharmacodynamic drug–drug interactions[d]

Object drug/drug class	Interacting drug/drug class	Outcome
ACE inhibitors	Potassium-sparing diuretics	↑ Potassium level
ACE inhibitors	Potassium supplements	↑ Potassium level
Anticholinergic	Anticholinergic	↑ Anticholinergic effect
Antihypertensive	NSAIDs	↓ Antihypertensive effect
CNS agents (e.g., diazepam)	CNS agents (e.g., codeine)	↑ CNS effect
Diuretics	NSAIDs	↓ Diuretic effect
NSAIDs, Aspirin	Corticosteroids	↑ Peptic ulcer risk
Verapamil	Beta blockers	↓ Heart rate
Warfarin	Antiplatelet agents	↑ Risk of bleeding
Antiplatelet agent	Antiplatelet agent	↑ Risk of bleeding

Arrow indicates the influence of the second (interacting) drug on the concentration of the first, object drug

[a] Clinically significant pharmacokinetic drug–drug interactions selected by Hanlon and Schmader [36]

[b] Clinically significant drug-drug interactions selected by Malone et al. [35]

[c] Other clinically important drug–drug interactions, not selected by Malone's panel, including an additional four drug–drug interactions we added [35]

[d] Clinically significant pharmacokinetic drug–drug interactions selected by Hanlon and Schmader, including additional two drug–drug interactions we added [36]

possibly leading to serious adverse events: combination of amiodarone with CYP3A4-metabolized HMG Co-A reductase inhibitors, i.e. either simvastatin or atorvastatin (acting by inhibiting CYP3A4, amiodarone increases the concentration of the two statins and leads to increased risk of rhabdomyolysis); combination of selective serotonin reuptake inhibitors with either tramadol or metoclopramide (both combinations could result in high serotonin levels and life-threatening serotonin syndrome); combination of clopidogrel with proton pump inhibitors (PPIs) (acting through CYP2C19 inhibition, PPIs decrease the formation of the clopidogrel-active metabolite and reduce its antiplatelet activity) (Table 5) [74–78].

Hanlon's adjunct to Malone's list contains overall 34 pharmacokinetic and nine pharmacodynamic drug–drug interactions in the elderly population. Among the pharmacodynamic interactions, a potential interaction between corticosteroids and NSAIDs (increased risk of peptic ulcer disease) was defined by Hanlon and Schmader [36]. The new protocol extends the list to potential interactions between aspirin and corticosteroids, also leading to the increased risk of peptic ulcer, and to potential interactions between two antiplatelet agents, resulting in increased risk of bleeding [74].

In total, 70 potentially clinically important drug–drug interactions were included in the new protocol.

Discussion and conclusion

There are numerous strategies aimed at improving drug-prescribing behavior to the elderly, which is the population most sensitive to adverse effects of drugs. These strategies include reducing the underuse, overuse, and misuse of drugs, as well as reducing potentially important drug–drug interactions. The overuse of drugs and polypharmacy, leading to increased risk of ADRs and drug–drug interactions,

can be avoided if only drugs with a clear indication, proven efficacy, and favorable risk-to-benefit profile are used [5, 18]. The overall number of drugs should be the smallest possible and the duration of treatment the shortest possible.

Potentially inappropriate medications represent one form of drug misuse. Numerous authors have concluded that avoiding PIMs reduces drug-related morbidity and mortality in elderly patients [2]. The use of explicit screening tools, as the most simple and easiest method of detecting PIMs, is expected to improve the quality of prescribing [4]. There are several tools currently available, each with a different degree of comprehensiveness and complexity and some with more advantages than others. As there are marked differences between the availability of drugs in different countries, we recommend that each country adapt the most acceptable screening tool. For European countries, adaptation of the French or German screening tools together with Beers criteria may be advisable.

However, no one screening tool can substitute for the prescriber's thorough consideration of each individual elderly patient. Appropriate prescribing in the elderly also includes all measures aimed at improving the patient's adherence to the therapy, including good communication between the prescriber and the patient, but also among all physicians involved in providing healthcare to that patient [3–5, 18, 79]. Reducing the use of PIMs is just one of the strategies that can be adopted for better and safer prescribing in the elderly, but all useful strategies should be implemented together.

The new protocol reported here, which combines the French, Beers, McLeod, and Lindblad criteria, represents a well-balanced and comprehensive tool that may be widely applied in the analysis of drug prescribing in the elderly (defined as 65 years or older). It could be argued that the present protocol contains drugs that have not been found to be potentially inappropriate by some other experts (i.e., amiodarone), but it follows both the Beers' criteria and the French panel. Although the McLeod criteria were developed back in 1997, the definition of inappropriate long-term NSAIDs use along with hypertension, chronic renal, or heart failure in these criteria is still relevant and should be part of screening tools for PIMs.

Table 5, which lists potentially clinically important drug–drug interactions, may seem complex and difficult to follow, but there are many potentially important drug–drug interactions and while reducing their number would make the tool easier to follow, it would result in very important adverse drug combinations being ignored.

In conclusion, the new protocol is able to detect potentially clinically important drug–drug interactions and PIMs in the elderly and suggests alternative therapeutic solutions. As PIMs and drug interactions are often overlaping, analyzing them within the same protocol will provide more comprehensive quality assessment of drug prescribing in the elderly and facilitate the detection of adverse outcomes caused by either PIMs or drug interactions. Both outcomes may in turn result in better prescribing practices. We expect the new tool to be used internationally by prescribers and pharmacists in ambulatory and clinical settings as well as in nursing homes. Combining North American and European tools together makes the tool applicable worldwide in the elderly population.

The sensitivity of our tool in detecting PIMs and in assessing PIM- or drug interaction-related morbidity and hospital admissions should be tested against other criteria in the real life environment.

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