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REVIEW

Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria

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Abstract

Purpose Potentially inappropriate medication (PIM) use causes preventable adverse drug reactions in older patients. Several assessment tools have been published to identify and avoid PIM use. In this systematic literature review, we aim to provide summaries and comparisons of validated PIMs lists published between 1991 and 2017 internationally.

Methods In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA), we performed a systematic review of articles describing the development and validation of criteria for identification of PIMs among older people published between January 1991 and April 2017. The searches were conducted on PUBMED, AgeLine, Academic Search, Academic Search Premier, and CINAHL. We identified the most common medications/classes described as PIM. We also identified the drug–disease interactions and drug–drug interactions reported among criteria.

Results From 2933 articles screened, 36 met our inclusion criteria. The majority used the Delphi method to validate their criteria. We identified 907 different medications/classes, 536 different drug disease interactions involving 84 diseases/conditions, and 159 drug–drug interactions. Benzodiazepines and nonsteroidal anti-inflammatory drugs were the medications most commonly reported as potentially inappropriate for older people.

Conclusion Although approaches aimed at detecting inappropriate prescribing have intensified in recent years, we observed limited overlap between different PIM lists. Additionally, some PIM lists did not provide special considerations of use and alternative therapies to avoid PIMs. These facts may compromise the use of PIM lists in clinical practice. Future PIM lists should integrate information about alternative therapies and special considerations of use in order to help clinicians in the drug prescription.

Keywords Inappropriate prescribing · Potentially inappropriate medication list · Drug-related side effects and adverse reactions · Aged

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Introduction

As the complexity of pharmacotherapy has increased with increasing medication use, particularly among older adults with multiple morbidities [1], medication risk management has become an increasingly important area of research. In this field, potentially inappropriate medication (PIM) is a term used to describe the use of a medicine for which the associated risks outweigh the potential benefits, especially when more effective alternatives are available [2]. PIM use is an important public health challenge, with high prevalence rates (from 18 to > 40%) across a variety of healthcare settings [3–6]. Notably, elderly patients are more likely to be exposed to PIMs because they often deal with age-related pharmacokinetic and pharmacodynamic changes, which can result in increased adverse drug reactions and decreased efficacy [7, 8]. Additionally, older patients often suffer from multiple chronic-degenerative diseases and therefore use a higher number of drugs, compared to other age groups [9]. In this population, PIM use can lead to avoidable adverse drug events (ADEs) [3, 10], including falls, fractures, and delirium and is associated with hospitalization [11–13] and mortality [14–16].

In recent years, many strategies and tools have been developed to assess the appropriateness of medication use in older people [2, 17–51]. Explicit criteria (EC) focusing on a single medication/medication class can support improvements to the quality of drug therapy and help to monitor drug therapy. However, the development of evidence-based PIM lists specifically for older populations is problematic, as older people are typically underrepresented or excluded from most efficacy and safety trials [52, 53]. Accordingly, some investigators have used a consensus technique that synthesizes accumulated expert opinion to develop EC that would facilitate the formulation of recommendations for suitable treatments in older people [54]. This consensus technique could be used to determine which statements from the literature are applicable in clinical practice [22].

Many different expert panels, including pharmacists, geriatricians, and other health professionals, have developed lists of EC to identify PIM use among older people in different countries [2, 17–51]. Previous systematic reviews identified 7–25 different PIM lists applied to older people [55–57]. Although Luchetti et al. [57] summarized and described all medications classified as PIMs using 14 validated and nonvalidated PIM lists published between 2006 and 2015, the literature lacks a comprehensive evaluation of the most common drug–disease and drug–drug interactions described in these validated PIM lists. Notably, summaries of the items proven valid by many consensus panels may facilitate a translational comparison of the processes and provide information about the most important PIMs in clinical practice, which would inform the development of interventions aimed at improving the prescription of specific medications. Therefore, in this review, we aim to summarize and compare the validated potentially inappropriate medications lists for older people published in different countries between 1991 and 2017. Additionally, we aim to summarize the medications and drug–disease and drug–drug interactions listed in the different potentially inappropriate medications lists.

Methods

This review was performed according to a standard protocol for systematic reviews, which was based on the methodological manuals of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The PRISMA checklist is available in Appendix 1.

Search strategy

We systematically identified studies published between January 1991 and April 2017 without any language restriction in the PUBMED and Academic Search Complete via EBSCOhost, Academic Search Premier via EBSCOhost, AgeLine via EBSCOhost, and CINAHL via EBSCOhost electronic databases. We selected this time limit for publication inclusion because the first instrument for PIM assessment was published in 1991 by Beers et al. [22]. The search included terms related to older adults or appropriate/inappropriate medication. Details of the full search strategy are included in Appendix 2.

Eligibility criteria

Original studies describing the EC used to determine potentially inappropriate medications were considered eligible for inclusion in this review if they involved individuals aged 65 years and older and described the development and validation of the methods used in the PIM list. Interventions and observational studies that evaluated PIMs were also retained if the abstract described potentially relevant PIM lists.

We applied the following exclusion criteria: medication review techniques using implicit criteria to evaluate PIMs and lists of PIMs restricted to specific therapeutic classes or specific diseases. Additionally, we excluded studies of PIMs not validated by expert consensus and guidelines or recommendations for the assessment of inappropriate prescriptions, as well as letters, editorials, and duplicate studies.

Study selection

Duplicate manuscripts were removed after exporting the search results to Endnote, version X6 (Clarivate Analytics, Philadelphia, PA, USA). Subsequently, two reviewers independently screened the titles and abstracts of the remaining

manuscripts to identify potentially relevant studies describing the development and validation of PIM lists. Additional studies were identified by a manual search of the citation lists for studies that detailed potentially relevant PIM lists. Finally, full-text copies of studies that described either the validation or use of any of the potentially relevant measures were retrieved and considered for inclusion in this review. If a decision could not be reached regarding the ability of a manuscript to meet the inclusion criteria, a decision was reached during the following selection round.

Data extraction and synthesis

Two authors (FRM and JSF) independently extracted the data, after which the first author checked the completeness by reviewing the extraction tables generated by the second author and checking the extracted data in the full-text articles. Disagreements were resolved by discussion between the two authors; if no agreement could be reached, a third author was consulted (VMV).

The following data were extracted from the selected articles: country of origin, source of data used, and validation method (consensus technique, expert panel, literature based). We also extracted aspects evaluated in the lists of PIMs (medications, dosage, duration of therapy, duplication, drug–disease interactions, drug–drug interactions). We also analyzed the medication/medication class names and drug–disease interactions (medication or medication dosage or medication duration with consideration of diagnosis) and drug–drug interactions reported in all PIM lists. We considered all medications belonging to a class as inappropriate if the authors described concerns about the medication class and did not describe single medications. However, the anticholinergic medication class exhibited considerable variation in terms of the selection of specific drugs. Therefore, we included anticholinergic drugs described in a recent review of the literature for the EC that did not specifically state which medicines were considered anticholinergic [58]. Additionally, we also considered a medication class as inappropriate when the authors described single medications and raised concerns related to the medication class.

The data were entered into Excel (Microsoft Corp., Redmond, WA, USA), and all individual medications reported in the studies were subsequently grouped into Anatomical, Therapeutic and Chemical (ATC) classes (five levels).

Results

The search strategy produced 2933 potentially relevant publications (Fig. 1). After screening titles and abstracts, we retained 248 potentially relevant publications according to the inclusion criteria. After a full-text review, 214 articles were excluded according to the exclusion criteria. A manual search from the reference lists of the included articles produced two relevant publications not found in the previous systematic database search. Thus, 36 articles were included in this systematic review [2, 17–51].

Table 1 describes the characteristics of the PIM lists evaluated in this review. Most studies were conducted in Europe [2, 23, 25, 26, 28–30, 35, 36, 38, 39, 42, 43, 47, 49] and North America [17–19, 21, 22, 27, 32, 37, 41, 45, 46, 48, 51]. However, other countries from Asia [24, 31, 33, 34, 40, 50], Oceania [20], and South America [44] such as Taiwan [24], Pakistan [40], South Korea [33, 34], Thailand [50], Japan [31] Australia [20], and Chile [44] have also published lists of PIMs.

The majority of the PIM lists (23 PIM list, 63.9%) are aimed at the general population aged 65 years and older. The Norwegian General Practice (NORGEP) criteria [47] and its adaptation for nursing home residents were designed especially for individuals aged 70 years and older [42] and the French criteria [36] for those aged 75 years and older. Only three PIM lists (8.3%) were developed for nursing home residents [22, 32, 42], two (5.5%) for older hospitalized patients [28, 40] and one (2.7%) for use in community pharmacies [49].

Some PIM lists, such as Beers (1991, 1997, 2003, 2012 and 2015) [17, 18, 21, 22, 27], STOPP (Screening Tool of Older People's Prescriptions) version 1 [29] (2008) and 2 (2015) [43], FORTA (Fit fOR The Aged) [35], Australian Prescribing Indicators Tool (2012) [20], Thailand criteria (2008) [50], and Lindblad criteria (2006) [37], used the current literature on efficacy and safety in older adults as an evidence base to develop their own list of PIMs. Other PIM lists, such as the McLeod criteria (1997) [41], Rancourt criteria (2004) [46], French criteria (2007) [36], NORGEP criteria (2009) [47], and PRISCUS (2010) [30], combined ECs previously published with a review of current literature. However, most PIM lists used previously published PIM lists to develop their lists of PIMs [2, 19, 23–26, 28, 31–34, 38–40, 42, 44–45, 48–49, 51]. Twenty-one (58.3%) of the 36 PIM lists were based on the Beers criteria and its updates, ten(27.8%) on the STOPP criteria and its update, and seven (19.4%) on the McLeod criteria. The tool developed by Tommelein et al. [49] was based on items derived from 14 different PIM lists (Table 1).

Of the 36 studies identified, 19 (52.8%) used the Delphi method and 14 (38.9%) used a modified Delphi method, to validate their ECs. Two studies used the RAND/UCLA [20, 49] (Research and Development/University of California, Los Angeles) process and the Italian criteria [38] used the Nominal Group Technique. The number of experts ranged from 4 to 62 and approximately 50.0% of the consensus panels included between 10 and 20 respondents. We observed a predominance of physicians and pharmacists whose practices concentrate on

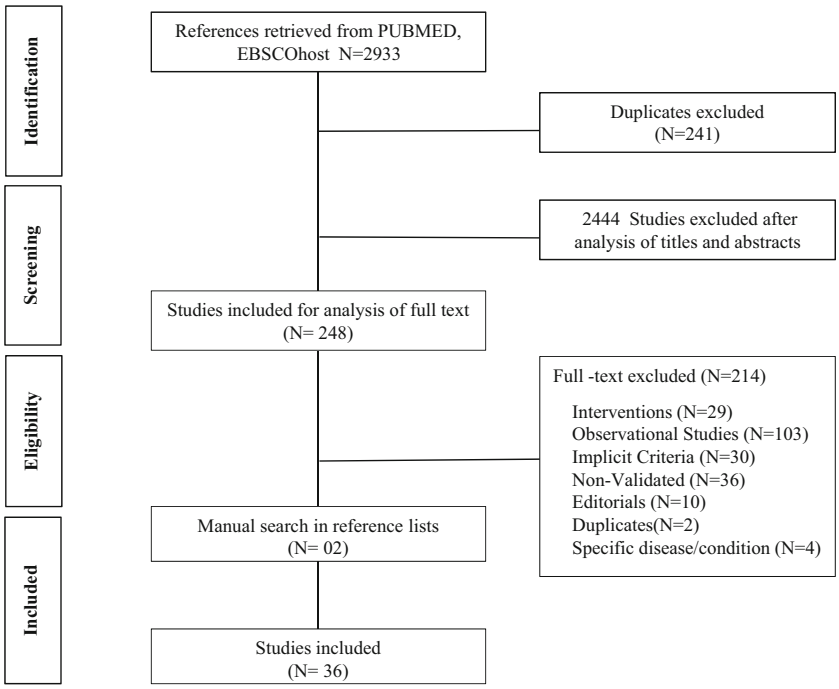

Fig. 1 PRISMA flow diagram of search strategy results

older adults and clinical pharmacology among the experts. Some studies included experts from different specialties such as psychiatrists [24, 30, 33, 38], cardiologists [24, 38], pulmonologists, gastroenterologists [24, 38], and urologists [24, 38] (Table 1).

Classification systems for PIMs varied between the studies. The majority of PIM lists provide an explicit listing of individual drugs. Eleven (30.6%) tools focused on PIMs to avoid in older adults independent of disease/condition; 22 (61.1%) included PIMs to avoid in older adults for specific diseases or conditions, and 20 (55.6%) mentioned relevant drug–drug interactions. Fourteen (38.8%) tools presented alternative therapies and 10 (27.8%) provided information about special considerations of use. Furthermore, 29 PIM lists (80.5%) also described doses or durations of medications, which should not be exceeded. Avoiding unnecessary duplication was mentioned in eight PIM lists (22.2%) (Table 2).

The 36 PIM lists identified a total of 907 different medications/ medication classes. Among them, only 4 classes and 44 medications were reported by more than 69% of PIM lists. The most prevalent class of medication identified as inappropriate was benzodiazepines, which were included in 33 (91.7%) of the 36 PIM lists. Other medication classes of PIMs identified included nonsteroidal anti-inflammatory drugs (NSAIDs) (28/36 PIM lists; 77.8%) followed by tricyclic antidepressants and antihistamines (27/36 PIM lists, 75.0%) (Table 3). Regarding the medications, only diazepam, chlordiazepoxide, indomethacin, and amitriptyline were considered inappropriate by 35 (97.2%) of the 36 PIM lists (Table 4).

Similar results were observed when we considered the 33 PIM lists (91.7%) that evaluated PIM independent of disease/condition. Benzodiazepines (29/33 PIM lists, 87.9%) and antihistamines (23/33 PIM lists, 69.7%) were the most common medication classes reported followed by tricyclic antidepressants (19/33 PIM lists, 57.6%) (Table 3). The commonest medications included were diazepam, chlordiazepoxide (31/33 PIM lists, 93.9%), amitriptyline, and chlorpheniramine (28/33 PIM lists, 84.8%) (Table 4).

Medications that can be avoided in individual diseases/conditions are specified in 22 PIM lists (61.1%). The most common medication classes implicated were NSAIDs (20/22 PIM lists, 90.9%), tricyclic antidepressants (19/ 22 PIM lists, 86.4%), followed by urologic spasmolytics, and long-acting benzodiazepines (18/22 PIM lists, 81.8%) (Table 3). Oxybutynin, diazepam, and chlordiazepoxide were the most common medications; they were reported as PIMs in specific diseases/conditions in 20 (90.9%) of 22 PIM lists (Table 4).

We identified 536 different drug–disease interactions involving 84 diseases/conditions. Among them, only 38 (7.0%) drug–disease interactions were cited in more than 25% of PIM lists. The most common conditions cited were constipation/chronic constipation (42/536 drug–disease interactions, 7.8%), dementia/cognitive impairment (41/536 drug–disease interactions, 7.6%), insomnia (36/536 drug–disease interactions, 6.7%), lower urinary tract symptoms/benign prostatic hyperplasia (28/536 drug–disease interactions, 5.2%), heart failure (19/536 drug–disease interactions, 3.5%), and history of falls/fractures (19/536 drug–disease interactions,3.5%). Table 5 summarizes the most common drug–disease interactions identified. The use of NSAIDs in patients with renal insufficiency (15/22 PIM lists, 68.1%) and heart failure (13/22 PIM lists, 59.1%)) and the use of metoclopramide in patients with Parkinson's disease

Table 1 Characteristics of potentially inappropriate medication (PIM) lists

Author	List name	Country	Population	Validation method	Number of experts	Characteristics of experts	Structure	Categories	Based
Beers et al. 1991 [22]	Beers criteria	USA[a]	Nursing home residents aged ≥ 65 years	Delphi method (two-round)	13	Expertise in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology, general clinical geriatrics, long-term care	30 criteria statements	19 medications or medication classes to avoid in the elderly; 11 criteria describing doses, frequencies, or durations that should not be exceeded.	Literature review
Stuck et al. 1994 [48]	Stuck criteria	USA[a] and Canada	Community-residing older persons ≥ 65 years	Modified Delphi method (two-round)	13	Geriatricians and pharmacists	27 criteria statements		Beers criteria 1991
Beers et al. 1997 [21]	Beers criteria	USA[a]	Persons aged ≥ 65 years	Modified Delphi method (two-round)	6	Expertise in general geriatrics, clinical pharmacology, pharmacoepidemiology, clinical pharmacy, psychopharmacology	63 criteria statements classified as having high severity or not	28 criteria describing potentially inappropriate	medications/class independent of diagnoses 35 criteria describing potentially inappropriate medications/class to be avoided in 15 diseases/-conditions
Literature review									
McLeod et al. 1997 [41]	Mcleod criteria	Canada	Persons aged ≥ 65 years	Modified Delphi method (two-round)	33	7 clinical pharmacologists, 9 geriatricians, 8 family practitioners, 8 pharmacists	38 criteria statements	18 contraindicated drugs in specific conditions 4 drug–drug interactions 16 drug–disease interactions	Beers criteria 1991 and literature review about drug–drug interactions
Zhan et al. 2001 [51]	Zhan criteria	USA[a]	Community-dwelling persons aged ≥ 65 years	Modified Delphi method (two--rounds)	7	5 geriatricians, 1 pharmacoepidemiologist, 1 pharmacist	33 drugs	11 drugs that should always be avoided 8 drugs that are rarely appropriate 14 drugs that have some indications for use in an elderly population	Beers criteria 1997
Fick et al. 2003 [27]	Beers–Fick criteria	USA[a]	Persons aged ≥ 65 years	Modified Delphi method (three--round)	12	Expertise in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology, and clinical geriatric medicine.	68 criteria statements classified as having high or low severity	48 criteria describing potentially inappropriate medications 20 diseases or conditions and medications to be avoided in these diseases/-conditions	Beers criteria 1997 and literature review
Rancourt et al. 2004 [46]	Rancourt criteria	Canada		Modified Delphi	4		111 criteria		Beers criteria 1991 and 1997, Mcleod criteria

Table 1 (continued)

Author	List name	Country	Population	Validation method	Number of experts	Characteristics of experts	Structure	Categories	Based
			Persons aged ≥ 65 years in long-term care	method (two-round)		1 general practitioner with a geriatric practice, 1 family physician (LB), 1 clinical pharmacist and 1 pharmacoepidemiologist		39 potentially inappropriate medication/ class 15 potentially inappropriate duration 20 potentially inappropriate dosage 37 drug–drug interactions or drug duplication	1997, and literature review of pharmacoepidemiological studies
Pugh et al. 2006 [45]	HEDIS[b]	USA[a]	Persons aged ≥ 65 years	Modified Delphi method	–	–	42 criteria	3 categories: Always Avoid, Rarely Appropriate, and Some Indications.	Beers–Fick criteria 2003
Lindblad et al. 2006 [37]	Lindblad criteria	USA[a]	Persons aged ≥ 65 years	Modified Delphi method (two-round)	9	2 geriatricians and 7 pharmacists	28 clinically important drug–disease interactions		Literature review
Laroche et al. 2007 [36]	French criteria	France	Persons aged ≥ 75 years	Delphi method (two-round)	15	5 geriatricians, 5 pharmacologists, 2 pharmacists, 2 general practitioners, 1 pharmacoepidemiologist	34 inappropriate practices in prescribing	29 medications or medication classes that should be avoided 5 drug–disease interactions	Beers criteria 1991 and 1997; Beers–Fick criteria 2003, McLeod criteria 1997; the criteria adapted to French practice (2001) and the guidelines of the French Medicine Agency on medication prescribing in the elderly.
Imai et al. 2008 [31]	Japanese beers criteria	Japan	Persons aged ≥ 65 years	Modified Delphi method (three--round)	9	Expertise in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology, and clinical geriatric medicine	47 medications or medication classes that should be generally avoid for all elderly patients		Beers–Fick criteria 2003
Gallagher et al. 2008 [29]	STOPP[c] version1	Ireland	Persons aged ≥ 65 years	Delphi method (two-round)	18	9 teaching hospital consultants in geriatric medicine, 3 clinical pharmacologists, 1 old age psychiatric, 2 senior academic primary care physicians, 3 senior hospital pharmacists with interest in geriatric pharmacotherapy	65 practice statements		Literature review
Winit-Watjana et al. 2008 [50]	Thailand criteria	Thailand	Persons aged ≥ 65 years	Delphi method (three--round)	17/16	Geriatricians, geriatric medicine lecturers or physicians working in the geriatrics area	77 practice statements	33 medications or medication classes with potential adverse reactions 32 drug–disease interactions	Literature review

Table 1 (continued)

Author	List name	Country	Population	Validation method	Number of experts	Characteristics of experts	Structure	Categories	Based
								12 drug–drug interactions	
Rognstad et al. 2009 [47]	NORGEP[d]	Norway	Persons aged ≥ 70 years in general practice	Delphi method (three--round)	57/47	14 clinical pharmacologists, 17 geriatricians, 16 general practitioners	36 criteria for pharmacologically inappropriate prescribing in general practice	21 criteria concerning single drugs and dosages 15 criteria concerning drug combinations to be avoided	Beers criteria 1991 and 1997, Beers–Fick criteria 2003, and Swedish recommendations, Norwegian studies and literature.
Kim et al. 2010 [33]	Korean criteria	Korea	Persons aged ≥ 65 years	Delphi method (two-round	14	14 geriatric specialists, including 7 family medicine specialists, 3 psychiatrists, 1 neurologist, and 3 clinical pharmacists		57 potentially inappropriate drugs for the elderly, independent of diagnosis 93 potentially inappropriate drugs in 29 diagnoses	Beers criteria 1991, and 1997, Beers–Fick criteria 2003, Zhan criteria 2001 and one phamacoepidemiological study
Maio et al. 2010 [38]	Italian criteria	Italy	Persons aged ≥ 65 years (outpatients)	A nominal group technique	9	3 general practitioners, 1 geriatrician, 1 clinical pharmacist, 2 psychiatrists, 1 cardiologist, 1 director of long-term care facilities	23 potentially inappropriate drugs		Beers–Fick criteria 2003
Holt et al. 2010 [30]	Priscus	Germany	Persons aged ≥ 65 years	Modified Delphi method (two--rounds)	25/26	Experts represented eight different specialties: geriatric medicine, clinical pharmacology, general practice, internal medicine, pain therapy, neurology, psychiatry, and pharmacy.	83 potentially inappropriate medications		Beers criteria 1997, Beers-Fick criteria 2003, Mcleod criteria 1997; French criteria 2007 and literature review
Basger et al. 2012 [20]	Australian Prescribing Indicators Tool—APIT	Australia	Persons aged ≥ 65 years	RND/UCLA (two-round)	15/12	Geriatricians/pharmacologists, clinical pharmacists, disease management advisors to organizations that produce Australian evidence based therapeutic publications.	41 criteria		Literature review
Mann et al. 2012 [39]	Austrian criteria	Austria	Persons aged ≥ 65 years	Delphi method (two-round)	8	A general practitioner, a specialist in neurology, three specialists in internal medicine, a psychiatrist, and two clinical pharmacists working in hospital pharmacies	73 drugs to avoid in older patients because of an unfavorable benefit/risk		Priscus 2010
American Geriatrics Society, 2012 [17]	Beers criteria	USA[a]	Persons aged ≥ 65 years	Modified Delphi method (two-round)	13	Expertise in geriatric medicine, nursing, pharmacy practice, research and quality measures	63 criteria statements classified as having high or low severity	34 medications or medication classes to avoid in the elderly 14 diseases and conditions and medications to	Literature review

Table 1 (continued)

Author	List name	Country	Population	Validation method	Number of experts	Characteristics of experts	Structure	Categories	Based
								be avoided in these conditions 13 medications to be used with caution in older adults	
Bachyrycz et al. 2012 [19]	New Mexico criteria	USA[a]	Persons aged ≥ 65 years	Delphi method (two-round)	12	Clinical pharmacists, geriatricians, nurses, managed care specialists, and consumers	72 drugs to be used with caution in the elderly		Beers–Fich 2003
Chang et al. 2012 [24]	Taiwan criteria	Taiwan	Persons aged ≥ 65 years	Modified Delphi method (two-round)	21	Geriatricians, neurologists, psychiatrists, cardiologists, pulmonologists, gastroenterologist, urologists, and clinical pharmacists	36 criteria	24 drug or drug classes to be generally avoided in older adults irrespective of comorbidities, 12 chronic conditions with 6 drug or drug classes that patients with these conditions should avoid.	Beers–Fick 2003; McLeod criteria 1997; Rancourt 2004; French criteria 2007, STOPP[c] version1; NORGEP[d] 2009; Thailand criteria 2008
Castillo-Páramo et al. 2013 [23]	Castillo-Páramo criteria	Spain	Persons aged ≥ 65 years in primary care	Delphi method (two-round)	19	Expertise in geriatric medicine and pharmacotherapy in older people	65 criteria		STOPP[c] version 1
Clyne et al. 2013 [25]	Clyne criteria	Ireland	Persons aged ≥ 65 years in primary care	Delphi method (two-round) + focus group	5	2 general practitioners 2 pharmacists 1 physician	34 criteria		Mcleod 1997 improved prescribing in the elderly tool (IPET), Beers criteria 2012, Prescription Peer Academic Detailing (Rx-PAD) study, Assessing Care of Vulnerable Elders (ACOVE), and STOPP[c] version 1
Fialova et al. 2013 [26]	Czech national criteria - CNC	Czech Republic	Persons aged ≥ 65 years	Modified Delphi method (three rounds)	15	Experts from the fields of geriatrics, internal medicine, general practitioners, clinical pharmacy, and clinical pharmacology	121 criteria	74 criteria for medications potentially inappropriate in old age 46 criteria for drug–disease interactions	Explicit criteria published between 1997 and 2011
Kunh-Thiel et al. 2014 [35]	FORTA[e]	Germany and Austria and Switzerland	Persons aged ≥ 65 years	Delphi method (two-round)	20	17 geriatric internists and 3 geriatric psychiatrists from Germany and Austria	225 drugs ranged from A (indispensable) to D (avoid) depending on the state of evidence for safety, efficacy and overall age--appropriateness	A: 55 drugs that are indispensable B: 60 drugs that are beneficial C: 67 drugs that are questionable D: 43 drugs that should be avoided.	Literature review

Table 1 (continued)

Author	List name	Country	Population	Validation method	Number of experts	Characteristics of experts	Structure	Categories	Based
Galán- Retamal et al. 2014 [28]	Galán- Retamal criteria	Spain	Patients hospitalized ≥ 65 years	Delphi method (two-round)	–	Pharmacists and general practitioners	50 criteria		Beers criteria 2012, STOPP[c] version 1 and Priscus
American Geriatrics Society 2015 [18]	Beers criteria	USA[a]	Persons aged ≥ 65 years	Modified Delphi method (two-round)	13	Expertise in geriatric medicine, nursing, pharmacy practice, research and quality measures	101 criteria statements classified as having high or low severity	40 medications or medication classes to avoid in the elderly 12	diseases/conditions and medications to be avoided in these conditions 16 medications/class medications to be used with caution 13 drug–drug interactions 20 medications inappropriate based on kidney function
Literature review									
Renon- Guiteras et al. 2015 [2]	EU (7) PIM list[f]	Europe	Persons aged ≥ 65 years	Delphi method (two-round)	27	14 geriatricians, 3 pharmacists, 7 clinical pharmacologists, and other 9 medical specialists	282 drugs/drug class and preparations were classified as medication inappropriate		Priscus 2010, French criteria 2007, STOPP[c] version 1, Beers 1997 e 2012, Beers–Fick, Mcleod 1997 and Micromedex
Kim et al. 2015 [34]	Kim criteria	South Korea	Persons aged ≥ 65 years	Delphi method (two-round)	20	14 Physicians and 6 pharmacists who had experience in a wide range of specialties across the internal medicine, mental health, neurology, gerontology, preventive medicine, urology, family medicine, rheumatology, and clinical pharmacy fields, and who have been working in general hospitals or universities as clinical practitioners and/or researchers.	Twenty-six drug ingredients belonging to seven drug classes		Beers 2012, STOPP[c] version 2, and Priscus 2010
Nyborg et al. 2015 [42]	NORGEP—NH[g]	Norway	Nursing home residents aged ≥ 70 years	Delphi method (three--round)	62/49	Specialists in geriatrics or clinical pharmacology, physicians in nursing homes and experienced pharmacists	34 criteria	11 single substance criteria 15 drug–drug combination criteria 8 criteria where regular consideration of describing	NORGEP[d] 2009
O'Mahony et al. 2015 [43]	STOPP[c] version 2	Europe	Persons aged ≥ 65	Delphi method (two-round)	19	Expertise in geriatric medicine and pharmacotherapy in older people	81 criteria		Literature review
Passi et al. 2016 [44]	Chilean criteria	Chile	Persons aged ≥ 65 years	Delphi method	–	Pharmacologists and geriatricians	265 medications	19 drugs that should always be avoided 47 drugs that are rarely appropriate 49 drugs that have some indications	Beers–Fick criteria 2003

Table 1 (continued)

Author	List name	Country	Population	Validation method	Number of experts	Characteristics of experts	Structure	Categories	Based
								for use in an elderly population and 150 drugs that can be used in elderly population	
Tommelein et al. 2016 [49]	GheOP3S[h]	Europe	Persons aged ≥ 65 years—community pharmacy	RAND/UCLA (two-round)	Part1:12 Part 2: 7	Part 1: 4 clinical pharmacists, 5 geriatricians, 2 general, 2 practitioners, 2 academics, 1 community pharmacist and 1 physician. Part 2: 7 community pharmacists ($N = 7$)	83 criteria	31 potentially inappropriate drugs independent of diagnosis 11 potentially inappropriate drugs dependent on diagnosis 29 drug–drug interactions 6 PPO 6 general care-related items to be addresses in the community pharmacy	14 different criteria, 3 explicit lists of prescribing indicators and one review study about drug–drug interactions
Khodykov et al. 2017 [32]	Khodykov criteria	USA[a]	Nursing home residents aged ≥ 70 years	Delphi method (three--round)	17/11	5 pharmacists, 5 nurses, 4 researchers, and 3 physicians	24 criteria	22 potentially inappropriate medications criteria 2 underused medications criteria	STOPP[c] version 2
Mazhar et al. 2017 [40]	Mazhar criteria	Pakistan	Patients hospitalized ≥ 65 years	Delphi method (two-round)	12	Part 1: geriatricians, resident doctors, clinical pharmacists, pharmacotherapy specialists and academic pharmacologists Part 2: specialists in geriatric medicine	32 criteria		Beers criteria 2015 and STOPP[c] version 2

[a] United States of America

[b] Healthcare Effectiveness Data and Information Set

[c] Screening Tool of Older Person's Prescriptions

[d] Norwegian General Practice criteria

[e] Fit fOR The Aged list

[f] European list of potentially inappropriate medications for older people

[g] Norwegian General Practice–Nursing Home criteria

[h] Ghent Older People's Prescriptions community Pharmacy Screening

Table 2 Summary of evaluated aspects in the potentially inappropriate medication (PIM) lists

List name	Year	Country	Independent of diagnoses	Dosage	Duration of therapy	Disease-Drug interaction	Drug- Drug interactions	Duplication	Alternatives Therapies s	Special considerations of use
Beers criteria	1991	USA[a]	■	■	■					
Stuck criteria	1994	USA/ Canada	■	■	■					
Beers-Fick criteria	2003	USA[a]	■	■	■	■				
McLeod criteria	1997	Canada			■	■	■		■	■
Beers criteria	1997	USA[a]	■	■	■	■				
Zhan criteria	2001	USA[a]	■							
Rancourt criteria	2004	Canada	■	■	■		■	■		
Lindblad criteria	2006	USA[a]				■				
HEDIS[b]	2006	USA[a]	■							
Japanese Beers criteria	2008	Japan	■	■	■					
French criteria	2007	France	■	■		■	■	■	■	
Thailand criteria	2008	Thailand	■			■	■			
STOPP[c] version1	2008	Ireland	■	■	■	■	■	■		
NORGEP[d]	2009	Norway	■	■			■			
Italian Criteria	2010	Italy	■	■	■					
Priscus	2010	Germany	■	■					■	■
Korean criteria	2010	Korea	■	■	■	■	■		■	
Taiwan criteria	2012	Taiwan	■	■		■	■		■	
Austrian Criteria	2012	Austria	■	■					■	
Australian Prescribing Indicators Tool	2012	Australia	■	■	■	■	■			
New Mexico criteria	2012	USA[a]	■	■					■	
Beers criteria	2012	USA[a]	■	■	■	■				■
Czech National criteria	2013	Czech Republic	■	■	■	■	■			
Clyne et al.	2013	Ireland	■	■	■	■	■			
Castillo-Paramo criteria	2013	Spain	■	■	■	■	■	■		
FORTA[e]	2009	Germany				■			■	
Galan - Retamal criteria	2014	Spain	■	■	■	■	■	■	■	■
STOPP version 2	2015	Europe	■	■	■	■	■	■	■	■
EU(7) PIM list[f]	2015	Europe	■	■	■	■			■	■
NORGEP- NH[g]	2015	Norway	■	■	■		■			■
Kim criteria	2015	Korea	■		■	■	■			
Beers criteria	2015	USA[a]	■	■	■	■	■			■
GheOP^{3}S[h]	2016	Europe	■	■	■	■	■		■	■
Passi et al.	2010	Chile	■						■	
Mazhar criteria	2017	Pakistan	■	■	■	■	■	■	■	■
Khodyakov criteria	2017	USA[a]	■	■	■	■		■		

[a] United States of America

[b] Healthcare Effectiveness Data and Information Set

[c] Screening Tool of Older Person's Prescriptions

[d] Norwegian General Practice criteria

[e] Fit fOR The Aged list

[f] European list of potentially inappropriate medications for older people

[g] Norwegian General Practice—Nursing Home criteria

[h] Ghent Older People's Prescriptions community Pharmacy Screening

(13/22 PIM lists, 59.1%) were the most commonly reported. Other prevalent drug–disease interactions included anticholinergic drugs in those with dementia/cognitive impairment (12/22 PIM lists, 54.5%), benzodiazepines in those with a history of falls/fractures (11/22 PIM lists, 50.0%), and urologic spasmolytics in those with lower urinary tract symptoms/benign prostatic hyperplasia (10/22 PIM lists, 45.4%).

We also identified 159 potential drug–drug interactions described in 20 PIM lists. Among them, only 16 (10.1%) drug–drug interactions were cited in more than 20% of PIM lists. The most common medication classes implicated were the NSAIDs (19/20 PIM lists, 95.0%), tricyclic antidepressants (14/20 PIM lists, 70.0%), followed by angiotensin-converting-enzyme inhibitors (12/20 PIM lists, 55.6%), and selective serotonin reuptake inhibitors (10/20 PIM lists, 50.0%). Regarding single medications, warfarin was the most common medication reported; it was included in 18(90.0%) of 20 PIM lists that evaluated drug–drug interactions. Table 6 describes the most common drug–drug interactions described. The concomitant use of warfarin with NSAIDs (11/20 PIM lists, 55.5%) and aspirin (7/20 PIM lists, 35.0%) was the most common drug–drug interactions reported followed by the concomitant use of NSAIDs and ACE inhibitors (7/20 PIM lists, 35.0%) and the concomitant use of beta blockers and verapamil (7/20 PIM lists, 35.0%).

Discussion

This systematic review presents data from 36 PIM lists (published between 1991 and April 2017) that developed and

Table 3 Most common medication classes reported in potentially inappropriate medication (PIM) lists

Medication class	All PIM[a] lists, *N* (%)	PIM[a] lists independent of disease/condition, *N* (%)	Drug–disease interactions, *N* (%)	Drug–drug interactions, *N* (%)
Total	36 (100.0)	33 (100.0)	22 (100.0)	20 (100.0)
Alimentary tract and metabolism				
Proton pump inhibitors	10 (27.8)	03 (9.1)	06 (27.3)	01 (5.0)
Gastrointestinal antispasmodics	24 (66.7)	14 (42.4)	15 (68.2)	06 (27.3)
Blood and blood forming organs				
Vitamin K antagonists	09 (25.0)	01 (3.0)	03 (13.6)	09 (45.0)
Direct thrombin inhibitors	12 (33.3)	04 (12.1)	03 (19.0)	07 (35.0)
Direct Factor Xa inhibitor	08 (22.2)	01 (3.0)	02 (9.1)	07 (35.0)
Cardiovascular system				
Alpha-adrenoreceptor antagonists	20 (55.5)	07 (21.2)	13 (59.1)	03 (15.0)
Thiazides diuretics	15 (41.7)	01 (3.0)	08 (36.4)	07 (35.0)
Loop diuretics	13 (36.1)	01 (3.0)	05 (22.7)	09 (45.0)
Potassium sparing diuretics	12 (33.3)	01 (3.0)	01 (4.5)	11 (55.5)
Beta blockers	15 (41.7)	00 (0.0)	09 (40.9)	10 (50.0)
Beta blockers (only nonselective)	17 (47.2)	01 (3.0)	11 (50.0)	10 (50.0)
Calcium channel blocker	16 (44.4)	00 (0.0)	12 (54.5)	07 (35.0)
Angiotensin-converting-enzyme inhibitor	15 (38.9)	01 (3.0)	06 (27.3)	12 (55.6)
Angiotensin II receptor blockers	12 (33.3)	00 (0.0)	06 (27.3)	07 (35.0)
Genitourinary system and sex hormones				
Estrogens	16 (44.4)	11 (33.3)	07 (31.8)	00 (0.0)
Urologic spasmolytics	20 (55.6)	06 (16.7)	18 (81.8)	07 (35.0)
Systemic hormonal preparations				
Corticosteroids	19 (52.8)	00 (0.0)	16 (72.7)	06 (30.0)
Musculo-skeletal system				
Nonsteroidal anti-inflammatory drugs	28 (77.8)	13 (39.4)	20 (90.9)	19 (95.0)
Muscle relaxants	12 (33.3)	05 (15.1)	07 (31.8)	05 (25.0)
Nervous system				
Opioid	12 (33.3)	04 (12.1)	06 (27.3)	08 (40.0)
Conventional antipsychotics	24 (66.7)	13 (36.4)	15 (68.2)	09 (45.0)
Atypical antipsychotics	19 (52.8)	04 (12.1)	06 (27.3)	05 (25.0)
Benzodiazepines long-acting	33 (91.7)	29 (87.9)	18 (81.8)	05 (25.0)
Benzodiazepines short-acting	29 (80.6)	25 (75.8)	16 (72.7)	05 (25.0)
Barbiturates	18 (50.0)	14 (42.4)	08 (36.4)	03 (15.0)
Nonbenzodiazepine hypnotics	12 (33.3)	07 (18.2)	05 (22.7)	03 (15.0)
Tricyclic antidepressants	27 (75.0)	19 (57.6)	19 (86.4)	14 (70.0)
Selective serotonin reuptake inhibitor	17 (47.2)	04 (12.1)	09 (40.9)	10 (50.0)
Respiratory system				
Antihistamines	27 (75.0)	23 (69.7)	16 (72.3)	07 (35.0)

[a] Potentially inappropriate medication

validated EC for identification of PIMs. The aggregation and comparison of studies showed a wide variability of PIMs, and we identified different 907 medications/medication classes reported in all PIM lists. A previous systematic review identified 729 different medications/classes described in 14 different PIM lists published between 2006 and 2015 [57]. The higher number of medications/classes in our review is justified by the fact that we included more years and other baseline data in our search strategies, and we did not exclude PIM lists for institutionalized or hospitalized patients or criteria that reported only drug–disease interactions. Furthermore, aspects such as different settings and prescribing cultures, differences in medication

Table 4 Most common medications reported in potentially inappropriate medication (PIM) lists

Medication	All PIM[a] lists, *N* (%)	PIM[a] lists independent of disease/condition, *N* (%)	Drug–disease interactions, *N* (%)	Drug–drug interactions, *N* (%)
Total	36 (100.0)	33 (100.0)	22 (100.00)	20 (100.0)
Benzodiazepines				
Diazepam	35 (97.2)	31 (93.9)	20 (90.9)	10 (50.0)
Chlordiazepoxide	35 (97.2)	31 (93.9)	20 (90.9)	10 (50.0)
Flurazepam	32 (88.9)	27 (81.1)	18 (81.8)	05 (25.0)
Clorazepate	31 (86.1)	24 (72.2)	17 (77.3)	04 (20.0)
Triazolam	29 (80.6)	21 (61.1)	19 (86.4)	10 (50.0)
Alprazolam	26 (72.2)	21 (61.1)	14 (63.6)	06 (30.0)
Oxazepam	25 (69.4)	20 (60.6)	14 (63.6)	04 (20.0)
Quazepam	25 (69.4)	18 (54.5)	14 (63.6)	10 (50.0)
Clonazepam	25 (69.4)	16 (48.5)	14 (66.7)	04 (20.0)
Nitrazepam	25 (69.4)	18 (54.5)	15 (68.2)	03 (16.7)
Nonsteroidal anti-inflammatory drugs				
Indomethacin	35 (97.2)	23 (69.7)	20 (90.9)	19 (95.0)
Piroxicam	31 (86.1)	19 (57.6)	20 (90.9)	19 (95.0)
Naproxen	29 (80.6)	16 (48.5)	19 (86.4)	18 (90.0)
Phenylbutazone	29 (80.6)	16 (48.5)	18 (81.8)	18 (90.0)
Meloxican	29 (80.6)	12 (36.4)	20 (90.9)	19 (95.0)
Ketoprofen	29 (80.6)	12 (36.4)	20 (90.9)	19 (95.0)
Ketorolac	28 (77.8)	15 (45.5)	20 (90.9)	18 (90.0)
Diclofenac	27 (75.0)	10 (30.3)	19 (86.4)	18 (90.0)
Celecoxibe	27 (75.0)	09 (27.3)	19 (86.4)	18 (90.0)
Ibuprofen	26 (72.2)	10 (30.3)	19 (86.4)	18 (90.0)
Tricyclic antidepressants				
Amitriptyline	35 (97.2)	28 (84.8)	20 (90.9)	14 (70.0)
Doxepin	28 (77.8)	22 (66.7)	18 (81.0)	13 (65.0)
Imipramine	26 (72.2)	17 (51.5)	19 (86.4)	14 (70.0)
Clomipramine	25 (69.4)	16 (48.5)	16 (72.7)	13 (65.0)
Antihistamines				
Chlorpheniramine	31 (86.1)	28 (84.8)	18 (81.0)	07 (35.0)
Promethazine	28 (77.8)	25 (75.8)	17 (77.3)	08 (40.0)
Hydroxyzine	27 (75.0)	24 (72.2)	11 (52.4)	08 (40.0)
Diphenydramine	27 (75.0)	24 (72.2)	16 (72.7)	07 (35.0)
Cyproheptadine	25 (69.4)	23 (69.7)	16 (72.7)	07 (35.0)
Gastrointestinal antispasmodics				
Hyoscyamine	26 (72.2)	16 (48.5)	15 (71.4)	07 (35.0)
Antipsychotics				
Thioridazine	26 (72.2)	16 (48.5)	17 (77.3)	09 (45.0)
Haloperidol	26 (72.2)	12 (36.4)	16 (72.7)	09 (45.0)
Urologic spasmolytics				
Oxybutynin	26 (72.2)	13 (39.4)	21 (95.5)	07 (35.0)
Selective serotonin reuptake inhibitor				
Fluoxetine	26 (72.2)	14 (42.4)	13 (59.1)	14 (70.0)
Opioid				
Pethidine/meperidine	26 (72.2)	15 (45.5)	12 (54.5)	13 (65.0)
Antiarrhythmic drugs				
Digoxin	27 (75.0)	19 (57.6)	08 (36.4)	05 (25.0)
Antihypertensive				
Nifedipine (short-acting)	27 (75.0)	14 (42.4)	12 (54.5)	07 (35.0)
Methyldopa	25 (69.4)	21 (63.6)	05 (23.8)	02 (10.0)

[a] Potentially inappropriate medication

availability/formulary between countries, and ethnopharmacology may have contributed to these results.

Conversely, we observed that less than half of PIM lists developed their own EC based on literature reviews. The development of evidence-based PIM lists is a dynamic and complex process, because older participants are commonly excluded from well-designed clinical trials [52, 53]. Thus, a majority of the studies used prior PIM lists to develop their own lists of PIMs [2, 19, 23–26, 28, 31–34, 38–40, 42, 44–45, 48–49, 51]. However, some of these authors have combined different PIM lists with drug references [2], pharmacoepidemiologic studies [25, 28, 33, 44], or

Table 5 Most common drug–disease interactions described in 22 potentially inappropriate medication (PIM) lists

Medication class/medication	Beers 1997	McLeod 1997	Beers–Fick 2003	Lindbad 2006	French criteria 2007	Thailand criteria 2008	STOPP[e] version 1	Korean criteria 2010	Beers 2012	APIT[f] 2012
Renal insufficiency										
NSAIDs[a]				x		x	x	x	x[c]	x
Heart failure										
NSAIDs[a]		x				x	x	x	x	x
Parkinson disease/Parkinsonism										
Metoclopramide			x	x		x	x	x	x	
Prochlorperazine							x		x	
Peptic ulcer										
Aspirin	x		x	x		x	x	x	x	
Non COX-2[b] selective NSAIDs	x	x	x				x		x	
NSAIDs[a]				x		x		x		
Cognitive impairment/dementia										
Anticholinergics drugs			x	x	x			x	x	x
Tricyclic antidepressants				x		x	x			
Urologic spasmolytics							x			
Benzodiazepines (all)				x	x				x	
Constipation/chronic constipation										
Anticholinergics drugs	x		x	x	x			x	x	
Tricyclic antidepressants	x		x	x		x	x		x	
Calcium channel blockers			x				x	x		
Urologic spasmolytics						x	x		x	
Opioids	x			x			x			
Lower urinary tract symptoms, benign prostatic hyperplasia										
Urologic spasmolytics			x				x	x		
Anticholinergics drugs			x	x	x			x	x	
Tricyclic antidepressants		x		x			x	x		
Falls										
Benzodiazepines (all)				x			x		x	x
Antipsychotics				x			x		x	x
Tricyclic antidepressants			x	x		x			x	x
Blooding disorders										
Aspirin	x		x			x	x	x		x
Dipyridamole	x		x			x	x	x		
Clopidogrel			x			x	x	x		
NSAIDs[a]	x		x			x		x		x
Glaucoma										
Tricyclic antidepressants		x				x	x	x		
Gout										
Thiazide		x					x	x		
Hypertension										
NSAIDs		x				x	x	x		
COPD										
Corticosteroids							x			
Nonselective beta blocker						x	x			x
Theophylline							x			

Table 5 (continued)

Medication class/medication	Beers 1997	McLeod 1997	Beers–Fick 2003	Lindbad 2006	French criteria 2007	Thailand criteria 2008	STOPP[e] version 1	Korean criteria 2010	Beers 2012	APIT[f] 2012
Diabetes										
Corticosteroids	x	x		x		x		x		
Insomnia										
Decongestants	x		x					x	x	
Methylphenidate	x		x					x	x	
Theophylline	x		x					x	x	

Medication class/medication	CNC[g] 2012	Taiwan criteria 2012	Clyne 2013	Castillo-Páramo 2013	Galán-Retamal 2014	FORTA[h] 2014	Kim 2015	Beers 2015	STOPP[e] version 2	GheOP3S[i] 2016	Mazhar 2017	Khodyakov 2017
Renal insufficiency												
NSAIDs[a]	x	x		x	x		x	x[c]	x		x	x
Heart failure												
NSAIDs[a]	x	x	x	x			x	x	x			
Parkinson disease/Parkinsonism												
Metoclopramide	x		x	x				x	x	x		x
Prochlorperazine			x	x				x	x			
Peptic ulcer												
Aspirin	x	x		x	x			x	x			
Non COX-2[b] selective NSAIDs		x	x	x				x	x			
NSAIDs[a]	x				x		x				x	x
Cognitive impairment/dementia												
Anticholinergics drugs	x	x						x	x	x		x
Tricyclic antidepressants	x		x	x			x		x			
Urologic spasmolytics	x		x	x			x		x			x
Benzodiazepines (all)		x					x	x				
Constipation/chronic constipation												
Anticholinergics drugs	x	x							x	x		
Tricyclic antidepressants	x		x	x			x					
Calcium channel blockers	x		x	x						x		
Urologic spasmolytics			x	x			x		x			
Opioids	x			x					x			
Lower urinary tract symptoms, benign prostatic hyperplasia												
Urologic spasmolytics	x		x	x	x		x		x			x
Anticholinergics drugs	x	x						x		x		
Tricyclic antidepressants	x		x	x			x		x			
Falls												
Benzodiazepines (all)	x	x	x	x			x	x	x			
Antipsychotics	x			x			x	x	x			
Tricyclic antidepressants	x						x	x				
Blooding disorders												
Aspirin		x		x					x			
Dipyridamole		x		x					x			
Clopidogrel				x					x			

Table 5 (continued)

Medication class/ medication	CNC[g] 2012	Taiwan criteria 2012	Clyne 2013	Castillo-Páramo 2013	Galán-Retamal 2014	FORTA[h] 2014	Kim 2015	Beers 2015	STOPP[e] version 2	GheOP3S[i] 2016	Mazhar 2017	Khodyakov 2017
NSAIDs[a]		x										
Glaucoma												
Tricyclic antidepressants		x[d]	x	x			x		x[d]			
Gout												
Thiazide		x	x	x				x	x	x		
Hypertension												
NSAIDs				x			x		x			
COPD												
Corticosteroids		x	x	x		x			x			x
Nonselective beta blocker		x		x						x		
Theophylline		x	x	x		x			x			
Diabetes												
Corticosteroids										x		
Insomnia												
Decongestants		x						x				
Methylphenidate		x						x				
Theophylline		x						x				

[a] Nonsteroidal anti-inflammatory drug

[b] Cyclo-oxygenase

[c] Chronic kidney disease stages IV and V

[d] Narrow-glaucoma

[e] Screening Tool of Older Person's Prescriptions

[f] Australian Prescribing Indicators Tool

[g] Czech national criteria

[h] Fit fOR The Aged list

[i] Ghent Older People's Prescriptions community Pharmacy Screening

Table 6 Most common drug–drug interactions described in 20 potentially inappropriate medication (PIM) lists

Drug–drug interactions	Mcleod 1997	Rancourt 2004	French criteria 2007	STOPP[e] version 2008	Thailand criteria 2008	NORGEP[f] 2009	Korean criteria 2010	APIT[g] 2012	CNC[h] 2012	Taiwan criteria 2012
Warfarin–NSAIDS[a]	x	x		x	x	x				
Warfarin + aspirin	x	x		x	x					
NSAIDs + ACEI[b]						x		x	x	
Beta blocker + verapamil		x		x					x	
NSAIDs + diuretic						x		x		
ACEI + potassium sparing diuretics		x			x	x			x	
Anticholinergic + anticolinergic			x							
NSAIDs + corticoids						x				
NSAIDs + anticoagulants							x		x	x
Aspirin + anticoagulants							x			x
NSAIDs + antiplatelet agent									x	
NSAIDs + SSRI[c]						x				
Warfarin–cimetidine	x	x			x		x			
TCA[d] + calcium channel blocker				x					x	
TCA + opioids				x					x	
Aspirin + NSAIDS					x			x	x	

Drug–drug interactions	Castillo-Páramo 2013	Clyne 2013	Galán- Retamal 2014	Beers 2015	Kim 2015	NORGEP—NH[i] 2015	STOPP[e] version 2015	GheOP3S[j] 2016	Mazhar 2017	Khodyakov 2017
Warfarin–NSAIDS[a]	x	x		x	x	x		x		
Warfarin + aspirin	x	x						x		
NSAIDs + ACEI[b]		x	x			x			x	
Beta blocker + verapamil	x		x				x		x	
NSAIDs + diuretic		x	x			x		x		
ACEI + potassium sparing diuretics						x		x		
Anticholinergic + anticolinergic				x			x	x		x
NSAIDs + corticoids				x		x	x	x		
NSAIDs + anticoagulants							x			x
Aspirin + anticoagulants			x				x		x	
NSAIDs + antiplatelet agent							x	x		x
NSAIDs + SSRI[c]		x				x		x		
Warfarin–cimetidine			x							
	x				x					

Table 6 (continued)

Drug–drug interactions	Castillo-Páramo 2013	Clyne 2013	Galán- Retamal 2014	Beers 2015	Kim 2015	NORGEP—NH[i] 2015	STOPP[e] version 2015	GheOP3S[j] 2016	Mazhar 2017	Khodyakov 2017
TCA[d] + calcium channel blocker										
TCA + opioids	x				x					
Aspirin + NSAIDS										x

[a] Nonsteroidal anti-inflammatory drug
[b] Angiotensin-converting enzyme inhibitors
[c] Selective serotonin reuptake inhibitor
[d] Tricyclic antidepressant
[e] Screening Tool of Older Person's Prescriptions
[f] The Norwegian General Practice criteria
[g] Australian Prescribing Indicators Tool
[h] Czech national criteria
[i] The Norwegian General Practice—Nursing Home criteria
[j] Ghent Older People's Prescriptions community Pharmacy Screening

prescribing indicators [28, 49] in order to include some medications and other instances of PIM use in older people (e.g., drug–drug interactions, drug class prescription duplication, special considerations of use, alternative therapies) which were not described in prior PIM lists.

We also verified that the majority of studies were developed for general practice. Few PIM lists focused on specific populations such as nursing home residents [22, 32, 42] and hospitalized patients [28, 40]. These were adaptations from existing PIM lists and included some new PIMs in their evaluation. For instance, some lists did not account for drugs frequently used during inpatient stays such as antibiotics. Thus, this result suggests that more work is needed to develop PIM lists for these populations and that some PIM lists originally designed for general practice could later be externally validated in these settings.

The Delphi technique was used to validate EC in the majority of the studies. This method is defined as an exercise in group communication that brings together and synthesizes the knowledge of a group of geographically distributed participants who have never meet [59]. Although there is no agreement on the definition of an expert, number of experts used, the number of rounds, and the consensus level in the literature, Delphi technique has some advantages over other consensus techniques such as the lack of discussion domination by any one panel member [60]. However, in this review, some studies [17, 18, 21, 27] modified the Delphi technique; these studies used a physical panel meeting at the end of consensus procedure in order to exchange views and resolve uncertainties.

We found that benzodiazepines and NSAIDs were the most common drugs reported as PIMs for older adults in all PIM lists. Previous systematic review also verified that these medication classes are among the most common reported in PIM lists [57]. However, these authors considered the number of indications of each medication class in each PIM lists while we evaluated the medication class included in each PIM lists. Of the 36 PIM lists evaluated, 33 described benzodiazepines as inappropriate. There is good observational data on the association between the use of benzodiazepine by older adults and serious ADEs, including impaired cognitive function [61, 62], delirium [63], respiratory insufficiency [64], falls [65], and fall-related injuries such as hip fractures [66]. Thus, they have the potential to create serious public health problems including hospitalization and death. Despite these risks, benzodiazepines are commonly used in the treatment of anxiety, depression, and insomnia in older patients around the world. Patients and providers hesitate to discontinue benzodiazepines because of the fear of withdrawal symptoms or relapse [67]. Studies show that there is a high prevalence of long-term use of this class in this age group, ranging 12 to 43% [68, 69].

There was very limited overlap between the PIM lists that we described in this study. Among all PIMs, only diazepam, chlordiazepoxide, indomethacin, and amitriptyline were

considered inappropriate by 35 of the 36 PIM lists. Furthermore, only 44 medications and 4 medication classes were present in 69.0% or more of PIM lists. Prior systematic reviews also reported that only a few drugs are common to all the lists of PIMs published [57]. The heterogeneity in the lists of medications reflects the fact that medication management in older adults is extremely complex with a very limited evidence base to guide it. Additionally, health professionals from various fields were involved in the development of the PIM lists and they would, therefore, have different approaches and attitudes. As a consequence, the list of medications can vary widely.

We compiled all drug–disease interactions and drug–drug interactions included in the different PIM lists. It is interesting to note that NSAIDs were the most common medication class in both types of drug interactions. Despite the consistent recommendations to avoid the use of this medication class in different situations, it is estimated that 40% of people aged 65 years and older fill one or more prescriptions for a NSAIDs each year [70] with additional users accessing NSAIDs over the counter [71]. This, like the high utilization of benzodiazepines, may highlight the limited impact of the consensus on PIMs or that, while potentially inappropriate, the benefit may frequently be determined to outweigh the risk for the individual.

We identified the drug–drug interactions described in 20 PIM lists. Although a considerable proportion of adverse drug reactions is caused by interactions between drugs [72, 73], drug–drug interactions are still underreported in the criteria for assessing inappropriate prescriptions in older adults. Of the 159 drug–drug interactions identified, only 16 are described in more than 20% of the PIM lists. The concomitant use of NSAIDs and aspirin with warfarin was the most frequent drug–drug interaction described. Many studies have provided an increased risk of hospitalization in elderly adults using this combination of drugs [72]. Additionally, the warfarin was the most common single medication reported among the drug–drug interactions lists. Despite this medication is highly effective in the prevention of stroke in atrial fibrillation, it is known for its interaction with many drugs [72–73], which is the leading cause of adverse drug event-related hospitalizations in older adults and can lead to fatal outcomes in this population [74].

Strengths

This is the first study that systematically compiled all drug–disease interactions and drug–drug interactions included in validated PIM lists since 1991. This systematic review used a comprehensive search strategy applied by the reviewers without language limitations. Furthermore, the study followed the PRISMA methodology, including study selection performed by two independent reviewers with arbitration by a third party if necessary. This reduced the risk of studies being omitted and also reduced the risk of selection bias.

Limitations

Our review had some important limitations. EC are limited in that they do not address individual differences among patients or the complexity or appropriateness of entire medication regimens. Furthermore, they need to be regularly updated in line with the evidence, and country-specific adaptations are necessary where countries differ in their guidelines, standards, and approved medications. It is important to recognize that a detailed description of the consensus method was not included in some studies [26, 42, 43]. To our knowledge, there is no formal method for quality assessment or risk of bias for consensus studies, so a rigorous assessment of the quality/bias of each study could not be performed as required by the PRISMA criteria [58].

Conclusion

Appropriate mediation management among older adults can help prevent serious adverse drug events [3, 10] which are associated with the increase of hospitalization and mortality in this population. For this reason, approaches aimed at detecting inappropriate prescriptions have intensified in the last decades with the development and validation of a number of strategies, particularly PIM lists. These PIM lists are important educational tools and should be included in the comprehensive assessment of every older patient who requires medication. We identified 36 different PIM lists. Different medication/medication classes, drug–disease interactions, and drug–drug interactions were included in different lists, with limited overlap between the PIM lists presented. These results demonstrate that the use of medications in older people is complex field and that more evidence is required to be able to generate consistent expert recommendations and to implement them.

Our review highlights the most common PIMs, drug–disease interactions, and drug–drug interactions validated by expert consensus for over 26 years. These results can help health professionals to elaborate strategies to minimize use of PIMS in many different settings. Although benzodiazepines and NSAIDs were the most common medications classified as being inappropriate, they are still commonly used in older adults. Avoiding medication in which the risks outweigh the benefits in the elderly patient continues to be a challenge for health professionals. Some PIM lists are complex and did not provide special considerations of use and alternative medications to avoid those considered potentially inappropriate. In addition, few PIM lists provide information that supports safely tapering or withdrawing PIM. These facts may compromise

the use of PIM lists in clinical practice. Future PIM lists should integrate information about alternative therapies and special considerations of use in order to help clinicians to make decisions about drug prescription.

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Author contributions FRM and VPM participated in all stages of this project, from the design and interpretation of data to its final writing. FRM and JSF conducted the development of search strategies, selection procedure, data extraction, data synthesis, and analysis. EVP contributed to the database organization and data extraction. SNH contributed to the critical review and writing of this manuscript. All authors participated in the discussions, result interpretation, and approved the final version of manuscript for submission.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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