European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-021-03145-6

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

REview of potentially inappropriate MEDIcation pr[e]scribing in Seniors (REMEDI[e]S): French implicit and explicit criteria

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Received: 13 November 2020 / Accepted: 15 April 2021

Abstract

Purpose To establish a consensus on both explicit and implicit criteria in order to identify potentially inappropriate prescribing (PIP) in French older people aged 75 years and over or 65 years and over with multimorbidity.

Methods Fifteen experts in geriatrics, general practice, pharmacy, and clinical pharmacology were involved in a two-round Delphi survey to assess preliminary explicit and implicit criteria based on an extensive literature review and up-to-date evidence data. Experts were asked to rate their level of agreement using a 5-level Likert scale for inclusion of criteria and also for rationale and therapeutic alternatives. A consensus was considered as reached if at least 75% of the experts rated criteria as "strongly agreed" or "agreed."

Results The new tool included a seven-step algorithm (implicit criteria) encompassing the three main domains that define PIP (i.e. overprescribing, underprescribing, and misprescribing) and 104 explicit criteria. Explicit criteria were divided into 6 tables related to inappropriate drug duplications ($n=7$ criteria), omissions of medications and/or medication associations ($n=16$), medications with an unfavourable benefit/risk ratio and/or a questionable efficacy ($n=39$), medications with an unsuitable dose ($n=4$) or duration ($n=6$), drug-disease ($n=13$), and drug-drug interactions ($n=19$).

Conclusion The REMEDI[e]S tool (REview of potentially inappropriate MEDIcation pr[e]scribing in Seniors) is an original mixed tool, adapted to French medical practices, aimed at preventing PIP both at the individual level in clinical practice and the population level in large-scale studies. Therefore, its use could contribute to an improvement in healthcare professionals' prescribing practices and safer care in older adults.

Keywords Older adults · Inappropriate prescribing · Implicit criteria · Explicit criteria · Delphi method · France

Introduction

The older population is more exposed to medications and more vulnerable to adverse drug events than the younger population due to several factors (e.g. multimorbidity and associated polypharmacy, age-related pharmacokinetic and pharmacodynamic changes, frailty) [1–3]. Between 10 and 30% of hospital admissions can be attributed to adverse drug reactions (ADRs) in older adults and more than half could be preventable [4]. So, optimizing medication use, notably by a limitation of inappropriate prescriptions, in the older population has become a public health challenge. Potentially inappropriate prescribing (PIP) is known to be associated with a range of negative health outcomes [1] and encompasses three main domains: underprescribing (failure to prescribe a clinically indicated medication in the absence of contraindications), overprescribing (prescribing more medications than clinically indicated and/or without a valid indication), and misprescribing (prescribing incorrectly a drug that is necessary) [5, 6]. Misprescribing may include (i) the use of potentially inappropriate medications (PIMs) defined as medications inducing an ADR risk exceeding their clinical benefit, particularly when more effective or safer alternatives are available; (ii) the use of medications with incorrect dose or duration; and (iii) medications that induce drug-disease or drug-drug interactions [6].

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Published online: 11 June 2021

Almost 50 tools have been developed to identify PIP and provide suitable recommendations for older adults [5, 7–9]. These tools can be grouped into three categories: explicit tools (criterion-based), implicit tools (judgment-based), and mixed tools that combine the two approaches. Explicit criteria rely on evidence-based data generally developed from a literature review, expert opinions, or consensus methods and include lists of medications to avoid regardless of the clinical conditions or in specific circumstances and medications to be introduced due to potential clinical benefits. In contrast, implicit criteria are based on clinical judgement and assess appropriateness of prescriptions at the individual level [6]. As for mixed tools, they allow combining the advantages of both implicit and explicit criteria [8]. Only a few mixed tools have been developed [5, 10, 11] while previous research has highlighted the need to combine the two approaches in order to successfully minimize harms associated with PIP [12]. Moreover, the combination of both implicit and explicit criteria is one of the 10 recommendations made by the International Group for Reducing Inappropriate Medication Use and Polypharmacy [13].

Since each country has different prescribing habits, guidelines, availability of drugs, and healthcare systems, there is also a need to develop country-specific criteria for an accurate assessment of inappropriate medication use [7]; this can explain the wide range of criteria published in the last decades. In France, a list of PIMs adapted to French practices was developed by consensus in 2007 (Laroche list) [14]. To remain valid, criteria must be regularly updated to consider the best evidence, marketing or withdrawal of medications [5]. Moreover, clinicians have pointed out the limitations of the French list based only on explicit criteria. Thus, it was necessary to adapt and update the French Laroche list, combining both explicit and implicit approaches, to help clinicians identify PIP in older people. In addition, from a public health perspective, revising the Laroche list was a prerequisite for quantifying PIP in France with updated data before implementing targeted-interventions aimed at reducing PIP.

Therefore, this study was conducted to reach a consensus, using the Delphi method, on implicit and explicit criteria for identifying PIP in French older adults aged 75 years and over or 65 years and over with multimorbidity.

Methods

Literature review: selection of implicit and explicit criteria

First, a literature review was conducted to identify previously published implicit and explicit criteria. This research was carried out in Medline, Scopus, and Cochrane Library databases. The most common medications reported as potentially inappropriate were mainly identified in prior and recent systematic reviews of explicit criteria [7, 15–18]. This selection targeted PIMs to avoid generally in older adults independently of clinical conditions and those to avoid in specific diseases or clinical conditions most frequently encountered in geriatric medicine. In addition, the omissions of certain medications were also identified in previous lists that integrated this aspect of inappropriate prescribing [19–23]. We also selected other PIMs and relevant drug-drug and/or drug-disease interactions most involved in adverse outcomes in the older population [24–31]. Secondly, for the identification of potential new criteria and/or for the updating of existing published criteria of interest, this literature review also included recommendations made by the French National Authority for Health (HAS) [32], the French Medicine Agency (ANSM), and the updated recommendations of French, European, or international societies in geriatric medicine or in specific medical fields. Systematic reviews and meta-analyses of randomized controlled trials or observational studies were also consulted, when necessary, to assess the level of evidence to qualify the inappropriateness of some PIMs. Moreover, therapeutic alternatives and/or recommendations for explicit criteria were also identified from this literature review (mainly from official French and/or European recommendations). Finally, as established in geriatric pharmacotherapy, these explicit criteria candidates addressed people aged 75 and over or 65 years and over with multimorbidity [33].

Development of preliminary implicit and explicit criteria

Based on the results of the literature review, a prescribing algorithm based on 7 implicit criteria and preliminary lists of explicit criteria grouped into 6 Tables were developed by a pharmacist and a clinical pharmacologist (BR and MLL).

The prescribing algorithm encompassed 7 implicit criteria or steps that aimed at providing guidance to clinicians for medication review and to identify PIP in older adults. The different steps to be evaluated were as follows: (1) check the presence of a valid indication for medications, (2) identify medications with an unfavourable benefit/risk ratio and/or a questionable efficacy, (3) identify medications with an inappropriate dose or duration, (4) ascertain the absence of potentially inappropriate drug-drug interactions, (5) identify medications that may exacerbate some clinical conditions, (6) check omissions of drugs and/or drug combinations, and (7) identify inappropriate drug duplications. For steps 2 to 7, recommendations referred to one of the 6 explicit criteria tables.

The preliminary explicit criteria included in each corresponding table were as follows: 35 criteria on medications with an unfavourable benefit/risk ratio and/or a questionable efficacy that should generally be avoided in older adults, 8 criteria on inappropriate dose ($n=4$) and duration ($n=4$), 16 criteria concerning potentially serious drug-drug interactions, 12 criteria on medications that could worsen chronic clinical conditions,

12 criteria on omissions of medications in specific diseases that needed to be treated/prevented and 3 criteria on omissions of associated medications in prevention of ADRs, and in the last table, 7 criteria on inappropriate drug duplications to be avoided due to potential serious harm and without additional benefit.

Delphi survey

We conducted a two-round Delphi survey, which is a common method used to gain a consensus opinion among experts where a lack of agreement or knowledge exists in a particular domain [34]. The Delphi method usually consists of two iterative rounds, with feedback to the panel of experts between rounds, until a consensus is reached, and using evidence-based literature as support [35]. This method was widely used for the development of explicit criteria for inappropriate prescribing in older adults [5, 34]. There is no international definition or specific guidance on the number of experts required for a Delphi survey; however, a panel of at least fifteen experts has been suggested as sufficient [36]. A heterogeneous panel should also be recommended in order to minimize bias results [34]. In addition, the median threshold to define consensus was estimated at 75% with a range between 50–97% [37].

Selection of experts

The panel of experts consisted of French healthcare professionals, with expertise in the field of drug prescribing in older adults. Fifteen experts including 5 geriatricians, 1 internist, 2 general practitioners, 2 pharmacists, and 5 clinical pharmacologists were invited to be on the panel. They were selected from different French geographic areas. No consent form was required to participate in this Delphi survey which was also anonymous.

First Delphi round

The first Delphi round was conducted from October 22 to November 15, 2019, using a web-based survey software (Sphinx®). Each expert received by e-mail all the instructions to fill in the web-based survey and the different documents to be evaluated. The first survey round concerned the seven-step prescribing algorithm, and the 93 explicit criteria divided into 6 tables. The participants were invited to grade the order of the different steps of the prescribing algorithm, suggest any modifications if necessary, and make comments. For each explicit criterion, participants indicated their opinion on a 5-point Likert scale from "strongly agree" to "strongly disagree." They also rated the rationale, the therapeutic alternatives, or the recommendations using the same grading system. They were prompted to make additional comments or modifications on each criterion and suggest new criteria and/or additional drug/drug classes within pre-existing criteria. For a given criterion, consensus was achieved if at least 75% of the participants selected as "strongly agreed" or "agreed." Criteria with at least 75% rating of "strongly disagreed" or "disagreed" were excluded. Levels of agreement were classified in four categories: very high (≥ 85%), high (84–75%), moderate (74–65%), and low (< 65%). After the first round, results were analyzed by BR and MLL. When no consensus was reached, explicit criteria were resubmitted for evaluation in the second round. In addition, new criteria proposed by the experts have been included where there was supporting evidence. To conclude, an overall synthesis including detailed responses and comments of experts was prepared for the second round.

Second Delphi round

During the second round (May 28 to June 15, 2020), experts were asked again to rate criteria for which a consensus had not been previously obtained in the first round. They were also asked to grade the criteria added during the first round. Moreover, they were invited to rate the rationale and the alternatives or recommendations for which no consensus had been reached in the first round and to do the same for new criteria added for inclusion in the second round. They were also invited to validate the new sequence of the prescribing algorithm steps and to suggest a name for this new French tool. After the second round, criteria with a level of agreement of < 75% were excluded from the final versions.

Results

Characteristics of experts

All the fifteen invited experts accepted to be on the panel and successfully completed the first and second rounds. The median age of the participants was 44 years (interquartile range (IQR) 40–51); 67% were women (Table 1). The panel of experts was equally balanced between physicians ($n = 8$) and pharmacists ($n = 7$). A high proportion (73%) worked in a hospital and the median number of working-year experience was 15 (IQR 12–25).

First Delphi round

Concerning implicit criteria, 80% of the participants agreed with the order of the steps proposed in the prescribing algorithm. As an improvement, implicit criteria were grouped into three categories which characterize PIP: overprescribing, underprescribing, and misprescribing. Therefore, the order of the steps was slightly modified.

Among the 93 explicit criteria proposed, 88 reached consensus for inclusion (≥ 75% of agreement) (Fig. 1; Table 2). Thus, 5 criteria did not reach consensus: antidementia drugs such as cholinesterase inhibitors (60%), memantine (60%), nitrofurantoin

Table 1 Characteristics of experts

Characteristics	
Sex, *n* (%)	
Male	5 (33.3)
Female	10 (66.7)
Age	
Mean (SD)	45.8 (10.2)
Median (IQR)	44 (40–51)
Min–Max	33–71
Professional, *n* (%)	
Physicians	
Geriatrician	5 (33.3)
Therapist	1 (6.7)
General practitioner	2 (13.3)
Pharmacists	
Hospital Pharmacist	1 (6.7)
Pharmacist (community)	1 (6.7)
Clinical pharmacologist	5 (33.3)
Place of work, n (%)	
Non-teaching hospital	1 (6.7)
University hospital	11 (73.4)
Ambulatory setting	3 (20.0)
Years of work experience	
Mean (SD)	18.5 (10.7)
Median (IQR)	15 (12–25)
Min–Max	5–40

(73%), and alpha-1 blockers for benign prostatic hyperplasia (73%) among medications with an unfavourable benefit/risk ratio and/or a questionable efficacy, and cholinesterase inhibitors and drugs with bradycardic effects (73%) among drug-drug interactions.

For the majority of criteria, the rating of the rationale was "very high" but for the alternatives, a certain level of disagreement was noted due to a lack of precision in the wording. In addition, 20 criteria were proposed by the experts: 8 criteria on medications with an unfavourable benefit/risk ratio and/or a questionable efficacy (immediate release calcium-channel blockers, statins and acid acetylsalicylic in primary prevention, phlebotonics, skeletal muscle relaxants, fluoroquinolones, long-acting hypnotic benzodiazepines (half-life > 20 h), antimigraine drugs with anticholinergic properties (i.e. flunarizine and pizotifene)); 1 criterion on duplications (concomitant use of two or more platelet aggregation inhibitors); 1 criterion on dose (tramadol); 1 criterion on duration (cotrimoxazole); 2 criteria on drug-disease interactions (nonsteroidal anti-inflammatory drugs (NSAIDs) and congestive heart failure, drugs that lower the seizure threshold and epilepsy); 6 criteria on drug-drug interactions (digoxin and thiazide/loop diuretics, concomitant use of 2 or more hyponatremic drugs, alpha-1 blockers and drugs with anticholinergic properties, lithium and NSAIDs, lithium and thiazide diuretics, lithium, and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)); and 1 criterion on omissions (optimal therapy in post-acute coronary syndrome). Then, 7 criteria were reclassified at the request of experts (e.g. nitrofurantoin initially included into the table on medications with an unfavourable benefit/risk ratio and/or a questionable efficacy was moved to the table on medications with an unsuitable duration). Moreover, as substantial modifications have been made for the wording of alternatives or recommendations, experts were invited to rate in the second round once more alternatives or recommendations of all criteria even if consensus has been reached in the first round for these statements. In total, this first round resulted in the inclusion of 111 explicit criteria for the second Delphi round.

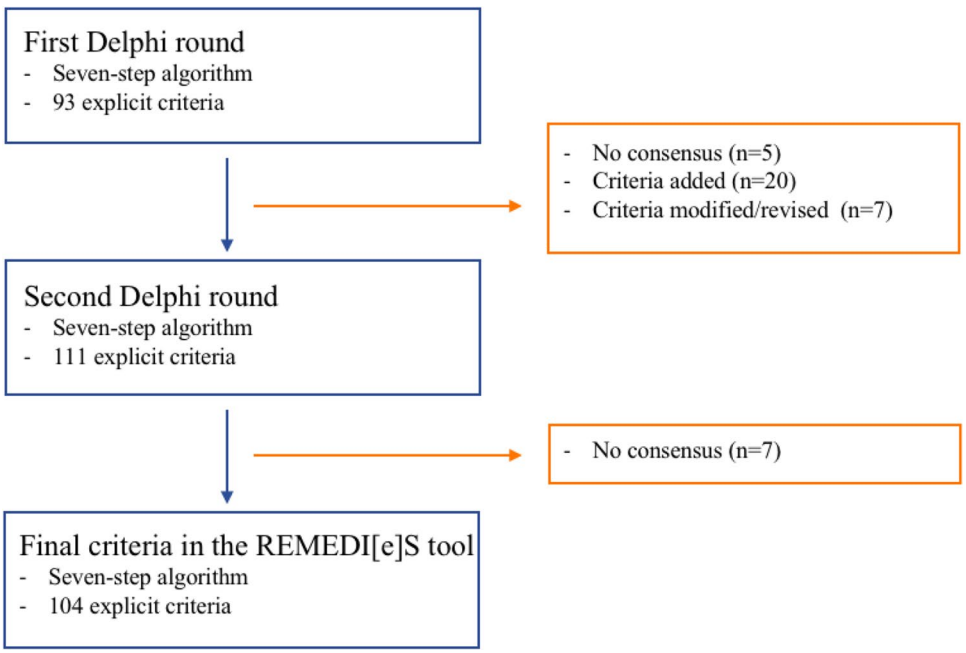

Fig. 1 Flow chart of Delphi rounds

Table 2 Experts' responses to consensus and levels of agreement for explicit criteria

Explicit criteria	Experts' responses					
	Inclusion [a]		Rationale[b]		Alternatives[c]	
	n / N total (%) [d]	Level of agreement [e]	n / N total (%) [d]	Level of agreement [e]	N / N total (%) [d]	Level of agreement [e]
Inappropriate drug duplications						
Concomitant use of 2 or more diuretics in arterial hypertension	15/15 (100)	Very High	15/15 (100)	Very High	13/15 (86.7)	Very High
Concomitant use of 2 or more inhibitors of the renin-angiotensin system	14/15 (93.3)	Very High	15/15 (100)	Very High	13/15 (86.7)	Very High
Concomitant use of 4 or more antihypertensive drugs	13/15 (86.7)	Very High	15/15 (100)	Very High	14/15 (93.3)	Very High
Concomitant use of 2 or more antiplatelet drugs	12/15 (80.0)	High	14/15 (93.3)	Very High	14/15 (93.3)	Very High
Concomitant use of 2 or more NSAIDs	14/15 (93.3)	Very High	15/15 (100)	Very High	14/15 (93.3)	Very High
Concomitant use of 2 or more different analgesics of the same step	14/15 (93.3)	Very High	13/15 (86.7)	Very High	14/15 (93.3)	Very High
Concomitant use of 2 or more psychotropic drugs of the same therapeutic class	15/15 (100)	Very High	14/15 (93.3)	Very High	13/15 (86.7)	Very High
Drug omissions						
Atrial fibrillation	15/15 (100)	Very High	NA		14/15 (93.3)	Very High
Resistant arterial hypertension (>150/90 mmHg)	15/15 (100)	Very High	NA		13/15 (86.7)	Very High
Chronic systolic heart failure	15/15 (100)	Very High	NA		13/15 (86.7)	Very High
Secondary prevention of acute coronary syndrome	13/15 (86.7)	Very High	NA		13/15 (86.7)	Very High
Chronic coronary syndrome	14/15 (93.3)	Very High	NA		14/15 (93.3)	Very High
Diabetes with microalbuminuria	14/15 (93.3)	Very High	NA		14/15 (93.3)	Very High
Major depression	15/15 (100)	Very High	NA		14/15 (93.3)	Very High
Primary open-angle glaucoma	14/15 (93.3)	Very High	NA		14/15 (93.3)	Very High
Chronic obstructive pulmonary disease	15/15 (100)	Very High	NA		14/15 (93.3)	Very High
Confirmed osteoporosis (Bone Mineral Density T-scores more ≤ -2.5) and/or history of fragility fractures	15/15 (100)	Very High	NA		14/15 (93.3)	Very High
Influenza vaccine	15/15 (100)	Very High	NA		15/15 (100)	Very High
Pneumococcus vaccine	15/15 (100)	Very High	NA		15/15 (100)	Very High
Zona vaccine	13/15 (86.7)	Very High	NA		12/15 (80.0)	High
Omissions of drug associations for the prevention of adverse effects						
Opioid treatment	15/15 (100)	Very High	NA		14/15 (93.3)	Very High
Long-term corticoids (>3 consecutive months with a dosage ≥ 7.5 mg/day prednisone equivalent)	14/15 (93.3)	Very High	NA		14/15 (93.3)	Very High
Weekly methotrexate treatment	14/15 (93.3)	Very High	NA		13/15 (86.7)	Very High
Medications with an unfavourable benefit/risk ratio and/or questionable efficacy						
Medications with anticholinergic properties						
First generation antihistamines	15/15 (100)	Very High	13/15 (86.7)	Very High	14/15 (93.3)	Very High
Antiarrhythmics (Class Ia)	15/15 (100)	Very High	14/15 (93.3)	Very High	12/15 (80.0)	High
Analgesics (step 1): nefopam	13/15 (86.7)	Very High	14/15 (93.3)	Very High	13/15 (86.7)	Very High
Antiemetics (excludes use in palliative care and post-chemotherapy)	13/15 (86.7)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Gastrointestinal antispasmodics	15/15 (100)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Tricyclic antidepressants	15/15 (100)	Very High	14/15 (93.3)	Very High	13/14 (92.9)	Very High
Antimigraine drugs	1/15 (6.7)	Low	14/15 (93.3)	Very High	8/15 (53.3)	Low
Antiparkinsonian agents	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Phenothiazine antipsychotics	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Antivertigo	15/15 (100)	Very High	14/15 (93.3)	Very High	14/15 (93.3)	Very High
Anxiolytics	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Hypnotics	14/15 (93.3)	Very High	13/15 (86.7)	Very High	14/15 (93.3)	Very High
Antitussives	14/15 (93.3)	Very High	14/15 (93.3)	Very High	14/15 (93.3)	Very High
Urinary antispasmodics	14/15 (93.3)	Very High	14/15 (93.3)	Very High	12/15 (80.0)	High
Other medications						
Antianginal agents: nicorandil	15/15 (100)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Centrally acting antihypertensives	15/15 (100)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Peripherally acting antihypertensives (alpha-1 blockers)	15/15 (100)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Immediate release calcium channel blockers	12/15 (80.0)	High	10/13 (76.9)	High	13/14 (92.9)	Very High
Statins in primary prevention of cardiovascular events	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Aspirin (≤375 mg/day) in primary prevention of cardiovascular events	14/15 (93.3)	Very High	14/15 (93.3)	Very High	14/15 (93.3)	Very High
Dipyridamole (excludes the injectable form for cardiovascular function testing)	14/15 (93.3)	Very High	13/15 (86.7)	Very High	15/15 (100)	Very High
Prasugrel	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Ticlopidine	14/15 (93.3)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Phlebotonics	14/15 (93.3)	Very High	13/15 (86.7)	Very High	14/15 (93.3)	Very High

Table 2 (Continued)

Explicit criteria	Experts' responses					
	Inclusion [a]		Rationale[b]		Alternatives[c]	
	n / N total (%) [d]	Level of agreement [e]	n / N total (%) [d]	Level of agreement [e]	N / N total (%) [d]	Level of agreement [e]
NSAIDs: indomethacin (excludes ophthalmic)	13/15 (86.7)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Skeletal muscle relaxants	13/15 (86.7)	Very High	15/15 (100)	Very High	11/14 (78.6)	High
Long- and short-acting sulfonylureas	14/15 (93.3)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Repaglinide	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Aluminium-based antacids (alone or in combination)	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Antidiarrheals: loperamide	13/15 (86.7)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
H2-receptor antagonists: cimetidine	14/15 (93.3)	Very High	14/15 (93.3)	Very High	13/15 (86.7)	Very High
Antiulcer: sucralfate	14/15 (93.3)	Very High	14/15 (93.3)	Very High	13/15 (86.7)	Very High
Laxative lubricants: paraffin oil	15/15 (100)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Stimulant laxatives	15/15 (100)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Fluoroquinolones	14/15 (93.3)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Long-acting anxiolytic benzodiazepines (half-life > 20 hours)	15/15 (100)	Very High	13/15 (86.7)	Very High	15/15 (100)	Very High
Long-acting hypnotic benzodiazepines (half-life > 20 hours)	14/15 (93.3)	Very High	14/14 (100)	Very High	13/15 (86.7)	Very High
Dopaminergic agonists (treatment of essential tremors)	13/15 (86.7)	Very High	13/15 (86.7)	Very High	15/15 (100)	Very High
Cholinesterase inhibitors	9/15 (60)	Low	12/14 (85.7)	Very High	10/15 (66.7)	Moderate
Memantine	8/15 (53.3)	Low	12/14 (85.7)	Very High	10/15 (66.7)	Moderate
Cerebral vasodilators	15/15 (100)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
5-alpha-reductase inhibitors	13/15 (86.7)	Very High	13/15 (86.7)	Very High	11/14 (78.6)	
Medications with an unsuitable dose and/or duration						
Unsuitable dose						
Colchicine >1.5 mg/day on the first day of treatment for acute gout	12/15 (80.0)	High	15/15 (100)	Very High	15/15 (100)	Very High
Digoxin >0.125 mg/day or digoxin serum concentration >1.2 µg/L	12/15 (80.0)	High	14/15 (93.3)	Very High	14/15 (93.3)	Very High
Tramadol >200 mg/day	13/15 (86.7)	Very High	14/15 (93.3)	Very High	11/15 (73.3)	High
Short or intermediate half-life benzodiazepines or nonbenzodiazepine hypnotics (Z-drugs) > half the dose given in young adults	14/15 (93.3)	Very High	14/15 (93.3)	Very High	12/15 (80.0)	High
Unsuitable duration						
Benzodiazepines >12 weeks (anxiolytic use)	15/15 (100)	Very High	14/15 (93.3)	Very High	13/15 (86.7)	Very High
Benzodiazepines and nonbenzodiazepine hypnotics (Z-drugs) >4 weeks (hypnotic use)	15/15 (100)	Very High	15/15 (100)	Very High	13/15 (86.7)	Very High
Colchicine for prophylaxis of acute gout >6 months	12/15 (80.0)	High	12/15 (80.0)	High	12/15 (80.0)	High
Cotrimoxazole >10 days (excludes treatment in the context of transplantation, prevention of infections in HIV-infected individuals)	12/15 (80.0)	High	11/15 (73.3)	Moderate	13/15 (86.7)	Very High
Proton pump inhibitors >8 weeks	13/15 (86.7)	Very High	15/15 (100)	Very High	14/15 (93.3)	Very High
Nitrofurantoin for curative treatment >7 days	15/15 (100)	Very High	14/14 (100)	Very High	12/15 (80.0)	High
Medications at risk of exacerbation of certain chronic and frequent clinical conditions						
Stable chronic heart failure						
Alpha-1 blockers for urinary incontinence (includes benign prostatic hyperplasia)	15/15 (100)	Very High	15/15 (100)	Very High	12/15 (80.0)	High
Nondihydropyridine calcium channel blockers	12/15 (80.0)	High	14/15 (93.3)	Very High	15/15 (100)	Very High
NSAIDs	13/15 (86.7)	Very High	15/15 (100)	Very High	13/15 (86.7)	Very High
Antiarrhythmics (class IV) in atrial fibrillation: dronedarone	14/15 (93.3)	Very High	13/14 (92.9)	Very High	15/15 (100)	Very High
Chronic constipation						
Drugs with anticholinergic properties	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Antihypertensives (centrally acting antihypertensives, calcium channel blockers)	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Peptic ulcers						
NSAIDs	14/15 (93.3)	Very High	14/15 (93.3)	Very High	14/15 (93.3)	Very High
Epilepsy						
Analgesics (nefopam, tramadol), fluoroquinolones, antidepressants, sedative antihistamines, benzodiazepines, cholinesterase inhibitors, conventional/atypical antipsychotics)	11/15 (73.3)	Moderate	12/14 (85.7)	Very High	9/14 (64.3)	Low
Major neurocognitive disorders						
Benzodiazepines and nonbenzodiazepines (Z-drugs)	14/15 (93.3)	Very High	14/15 (93.3)	Very High	14/15 (93.3)	Very High

Table 2 (Continued)

Explicit criteria	Experts' responses					
	Inclusion [a]		Rationale[b]		Alternatives[c]	
	n / N total (%) [d]	Level of agreement [e]	n / N total (%) [d]	Level of agreement [e]	N / N total (%) [d]	Level of agreement [e]
Drugs with anticholinergic properties	13/14 (92.8)	Very High	14/15 (93.3)	Very High	14/15 (93.3)	Very High
Conventional and atypical antipsychotics	12/15 (80.0)	High	13/15 (86.7)	Very High	13/14 (92.8)	Very High
Chronic renal failure						
NSAIDs	14/15 (93.3)	Very High	13/15 (86.7)	Very High	15/15 (100)	Very High
Chronic urinary retention (includes benign prostatic hyperplasia)						
Drugs with anticholinergic properties	14/15 (93.3)	Very High	14/15 (93.3)	Very High	14/15 (93.3)	Very High
Closed-angle glaucoma						
Drugs with anticholinergic properties	14/15 (93.3)	Very High	12/15 (80.0)	High	14/15 (93.3)	Very High
Inappropriate drug-drug interactions						
Drugs with bradycardiac properties (beta-blocker, digoxin, diltiazem, verapamil) + cholinesterase inhibitors (donepezil, galantamine, rivastigmine)	14/15 (93.3)	Very High	15/15 (100)	Very High	13/15 (86.7)	Very High
Digoxin + loop diuretic or thiazide diuretic	13/15 (86.7)	Very High	15/15 (100)	Very High	14/15 (93.3)	Very High
Oral anticoagulant (vitamin K antagonists, factor Xa inhibitors or direct thrombin inhibitors) + antiplatelet agents (including low dose aspirin: 50 mg to 375 mg/day)	14/15 (93.3)	Very High	15/15 (100)	Very High	13/15 (86.7)	Very High
Oral anticoagulant (vitamin K antagonists, factor Xa inhibitors or direct thrombin inhibitors) + NSAIDs	14/15 (93.3)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Vitamin K antagonists + antibiotics (macrolides, fluoroquinolones, cyclines, cotrimoxazole, cephalosporins (cefamandole, ceftriaxone, cefazolin, clindamycin))	15/15 (100)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Antiplatelet agents (includes low dose aspirin: doses of 50 to 375 mg/day) + NSAIDs	15/15 (100)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
NSAIDs (includes aspirin >375 mg/day) + corticosteroids	14/15 (93.3)	Very High	15/15 (100)	Very High	13/15 (86.7)	Very High
Statins (simvastatin, pravastatin, atorvastatin) + macrolides (azithromycin, erythromycin, clarithromycin, roxithromycin)	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
ACEI + potassium salts ACEI + potassium-sparing diuretics (amiloride, triamterene, eplerenone, spironolactone) ARB + potassium salts ARB + potassium-sparing diuretics (amiloride, triamterene, eplerenone, spironolactone) Potassium-sparing diuretics (amiloride, triamterene, eplerenone, spironolactone) + potassium salts	14/15 (93.3)	Very High	15/15 (100)	Very High	14/15 (93.3)	Very High
Cotrimoxazole + ACEI Cotrimoxazole + ARB Cotrimoxazole + potassium-sparing diuretics (amiloride, triamterene, eplerenone, spironolactone) Cotrimoxazole + potassium salts	13/15 (86.7)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
ACEI or ARB + NSAIDs (includes aspirin >375 mg/day)	14/15 (93.3)	Very High	14/15 (93.3)	Very High	15/15 (100)	Very High
Diuretics + NSAIDs (includes aspirin >375 mg/day)	14/15 (93.3)	Very High	15/15 (100)	Very High	15/15 (100)	Very High
Concomitant use of 2 or more hyponatremic drugs* (diuretics, TCA, SSRI, SNRI, mirtazapine, carbamazepine, oxacarbazepine)	12/15 (80.0)	Very High	13/15 (86.7)	Very High	13/15 (86.7)	Very High
Alpha-1 blockers (alfuzosin, doxazosin, silodosin, tamsulosin, terazosin) + drugs with anticholinergic properties	14/15 (93.3)	Very High	13/15 (86.7)	Very High	12/15 (80.0)	High
Concomitant use of 3 or more central nervous system depressant drugs (among antiepileptics, antipsychotics, benzodiazepines, antidepressants, opioids)	13/15 (86.7)	Very High	15/15 (100)	Very High	13/15 (86.7)	Very High
Concomitant use of 2 or more drugs with serotoninergic properties* (SSRI, SRNI, TCA, MAOI, mirtazapine, mianserin, tramadol, lithium)	14/15 (93.3)	Very High	14/15 (93.3)	Very High	13/15 (86.7)	Very High
Anticholinesterase drugs (galantamine, rivastigmine, donepezil, neostigmine) + drugs with anticholinergic properties	13/15 (86.7)	Very High	15/15 (100)	Very High	12/15 (80.0)	High
Concomitant use of 2 or more drugs with anticholinergic properties	14/15 (93.3)	Very High	14/15 (93.3)	Very High	13/15 (80.0)	High
Lithium + ACEI ou ARB	2/15 (13.3)	Low	14/15 (93.3)	Very High	11/15 (73.3)	Moderate
Lithium + thiazide or loop diuretics	2/15 (13.3)	Low	15/15 (100)	Very High	13/15 (86.7)	Very High
Lithium + NSAIDs	2/15 (13.3)	Low	15/15 (100)	Very High	12/15 (80.0)	High
Colchicine + macrolides (except spiramycin) or pristinamycin	13/15 (86.7)	Very High	14/15 (93.3)	Very High	13/15 (86.7)	Very High

ACEI angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *HIV* human immunodeficiency virus, *MAOI* monoamine oxidase inhibitor, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SSRIs* selective serotonin reuptake inhibitors, *SNRIs* serotonin-norepinephrine reuptake inhibitor, *TCAs* tricyclic antidepressants

Table 2 (Continued)

[a]Levels of agreement for the inclusion of criteria rated in the first round and for which a consensus has been reached during the first round. For criteria with no consensus reached in the first round or new criteria added in the second round, the levels of agreement indicated are those obtained in the second round

[b]Levels of agreement for the rationale of criteria rated in the first round or in the second round (for criteria initially proposed in the first round). For new criteria added in the second round, the levels of agreement indicated are those obtained in the second round

[c]Levels of agreement for alternatives or recommendations of criteria rated in the second round

[d]Proportions of experts (number of experts' responses/number of experts) who rated each criterion

[e]The level of agreement (strongly agreed or agreed) was categorized as low (<65%), moderate (65-74%), high (75-84%), and very high (≥85%). Consensus was achieved for criteria with high or very high levels of agreement

Second Delphi round

Consensus for inclusion was reached for all the explicit criteria except 7: drugs that lower the seizure threshold and epilepsy (73%), cholinesterase inhibitors (60%), memantine (53%), antimigraine drugs with anticholinergic properties (6.7%), and 3 criteria related to drug-drug interactions with lithium (13.3% with ACEI/ARB, NSAIDs, and thiazide diuretics) (Fig. 1; Table 2). All criteria with consensus had a "very high" or "high" rating for the alternatives and the rationale except for the rationale of cotrimoxazole used > 10 days ("moderate"). The final set of lists was composed of 104 explicit criteria: 7 inappropriate drug duplications (Online resource 1, Table 1), 13 omissions of medications and 3 omissions of medication combinations (Online resource 1, Table 2), 39 medications with an unfavourable benefit/risk ratio and/or a questionable efficacy (Online resource 1, Table 3), 4 and 6 medications with an unsuitable dose or duration, respectively (Online resource 1, Table 4), 13 frequent drug-disease interactions that could exacerbate chronic conditions (Online resource 1, Table 5), and 19 potentially serious drug-drug interactions (Online resource 1, Table 6). The seven-step prescribing algorithm was definitively validated by all experts (100% of the panel members agreed with the new order of the steps) (Online resource 1, Fig. 1). Combined with the algorithm, Tables 1 and 2 refer respectively to the "overprescribing" and "underprescribing" categories of inappropriate prescribing, while Tables 3, 4, 5, and 6 were grouped into the "misprescribing" category. Finally, a name was proposed for this new tool: "REMEDI[e]S" for "REview of potentially inappropriate MEDIcation pr[e]scribing in Seniors" (in French: "REvision des prescriptions MEDIcamenteuses potentiellement inapproprié[e]s chez les Seniors").

Criteria changes during Delphi rounds and compared to the French Laroche list

Criteria changes performed during Delphi rounds and for the development of the REMEDI[e]S tool compared to the original Laroche list are presented, in Online resource 2, Tables 1 and 2, respectively. In total, 50 criteria were added in the new tool compared to the Laroche list: 5 criteria about drug duplications, 15 criteria related to medications with an unfavourable benefit/risk ratio and/or a questionable efficacy, 5 criteria on drug-disease interactions, 18 criteria on drug-drug interactions, and 2 and 5 criteria related to unsuitable dose and duration, respectively (Online resource 2, Table 2).

Discussion

We propose a new French tool (REMEDI[e]S) combining implicit and explicit criteria designed to identify PIP in older adults aged 75 years and over or 65 years and over with multimorbidity. A consensus was achieved on a seven-step algorithm and 104 explicit criteria divided into six tables corresponding to the different domains of PIP (overprescribing, underprescribing, and misprescribing). The REMEDI[e]S tool may be considered as a comprehensive screening tool due to its mixed approach, the consideration of all domains of inappropriate prescribing, leading to a large range of criteria to detect efficiently PIP, and the provision of safer alternatives and/or recommendations for each explicit criterion.

Compared to the French Laroche list, established in 2007, the REMEDI[e]S tool presents significant modifications [14]. First, it is a combined tool that integrates both implicit and explicit approaches in contrast with the Laroche list that focused only on explicit criteria. The use of implicit criteria in the form of an algorithm may provide a comprehensive review of medications with a patient-centred approach and may allow addressing the complexity of drug regimens in the older population. In addition to this approach, explicit criteria can be used as decision support resources to facilitate the identification of inappropriate prescribing [8]. Therefore, our REMEDI[e]S tool may efficiently guide users in the process of detecting inappropriate prescribing and, thus, may constitute an optimal approach to improve medication use, as already highlighted by previous randomized controlled trials [12]. Secondly, we considered drug omissions in this new tool. In the literature, few existing tools focus on the underprescribing of medications with a valid indication [8, 9, 20, 38], while this domain of inappropriate prescribing may lead to unfavourable outcomes such as an increase of morbidity and mortality [39]. In addition,

a number of criteria were added due to their clinical relevance and supporting evidence since the development of the Laroche list in 2007 (e.g. proton-pump inhibitors if used superior to 8 weeks (PPIs), statins in primary prevention of cardiovascular events in adults aged > 75 years). In contrast, some criteria/medications initially in the Laroche lit were not selected in the REMEDI[e]S tool; in the majority, these are drugs that are no longer available on the French market. Moreover, some drugs and/or drug classes deemed potentially inappropriate in other international PIM lists were not considered for the consensus because their prescription prevalence is low (e.g. phenytoin) or because they are more often prescribed in specific conditions by specialists (e.g. phenobarbital, dopaminergic agents such as ropinirole or pramipexole, growth hormones). Similar to the Laroche list, safer alternative therapies and/or recommendations were proposed for each explicit criterion. The integration of alternatives was not systematically included in the different tools of explicit criteria [7, 9, 10]. Yet, providing pharmacological or non-pharmacological alternatives would further assist clinicians in making appropriate decisions regarding drug prescribing especially since the lack of therapeutic alternatives was reported as a barrier to use PIM lists in daily practice [40].

Consensus was achieved for the majority of criteria initially proposed in the first round and those added in the second round, except for rare criteria, in particular, those related to cholinesterase inhibitors and memantine. This disagreement illustrates the presence of conflicting opinions among the panel of experts regarding the use of these drugs; this controversy is also shared by scientific and medical communities. Although evidence supports that cholinesterase inhibitors and memantine may provide clinical benefits in older adults with dementia (improvement of cognition, function, and neuropsychiatric disorders), their efficacy seems limited, notably in long-term use [41]. However, these medications would provide benefit to some individuals, in particular in the short-term. A systematic review found that cholinesterase inhibitors were not significantly associated to a progressive reduction of mild cognitive impairment [42] while they exposed older adults to a range of adverse effects (gastrointestinal disorders, dizziness, syncope, etc.) likely to alter the quality of life [41, 42]. Therefore, few tools included anti-dementia drugs such as PIMs to be generally avoided in the older population, except the EU(7)-PIM list and the FORTA list where memantine was considered as a drug with questionable efficacy [43, 44]. Conversely, the FORTA list included cholinesterase inhibitors in the category of drugs with proven or obvious efficacy without limited extent of effect and/or safety concerns [44]. Other PIM lists considered that these should be avoided in specific clinical conditions, such as Parkinson disease [10, 45, 46], cardiac dysfunction [47], or syncope [48]. Thus, it emerges that the introduction or continuation of these drugs should particularly be discussed at the individual level, considering both the benefit-risk ratio and the preferences of patients with dementia and/or caregivers. Finally, in addition to anti-dementia drugs, 4 additional criteria were not retained by the majority of experts: anticholinergic antimigraine drugs (flunarizine, pizotifen) and three criteria related to drug-drug interactions with lithium. Experts' comments outlined that these criteria should be removed due to a low prevalence of use and/or their non-specificity in the older population.

Strengths and limitations

To create our tool, we used the Delphi method, a structured consensus technique extensively used to develop prescribing indicators [49]. This technique has the main advantage of allowing experts to express their opinion anonymously with no direct contact with other panelists and thus avoid any pressure to conform to the group's view and/or any influence by a panel member that may occur during face-to-face meetings [14, 34]. With the Delphi method, we included a panel of experts geographically dispersed and different healthcare settings, which provides a better overview of clinical practice in France [14]. We also used the consensus technique to rate implicit criteria that was a missing step in previous developments of implicit tools. In addition, our explicit criteria were classified according to therapeutic category, which may enhance their use in clinical practice and their implementation in electronic medical records [9].

However, our study also has some limitations. Although the Delphi method is commonly used for validating PIM lists, there is little evidence regarding its validity and reliability [50]. In fact, consensus results depend on the experts chosen and their expertise, and thus could be subjective, which may limit their reproducibility [34, 51]. Despite the fact that our tool allows the identification of PIP and provides alternatives, specific and accurate information that support safe tapering or withdrawing of medications judged as inappropriate in our criteria are not provided while they may be also of great usefulness to assist clinicians in optimizing drug prescribing in clinical practice [7]; we considered that clinicians should refer to existing deprescribing guidelines for this step. In addition, we point out that there is substantial physiological heterogeneity in older adults, and thus, the benefit/risk ratio of medications may differ between individuals [5]. This finding outlines the need to consider the clinical conditions at the individual level and highlights the importance of implicit criteria. Therefore, our explicit criteria are not intended to replace clinical judgment, which should always be considered first and should be in line with goals of care, patient values, and preferences. Finally, like other country-specific PIM lists, the content of our tool should be regularly updated in line with evidence and changes of medications on the French market to ensure its validity [8].

Future use in clinical practice, training, and research

The REMEDI[e]S tool may be used in the following way. First, it may be useful to assist healthcare professionals in their daily

clinical practice in assessing prescribing quality for older people at the individual level, in different healthcare settings (except in end-of-life and palliative settings). The tool is intended to be easy to use by integrating a seven-step prescribing algorithm referring to different sets of explicit criteria. In addition to existing deprescribing guidelines, our tool may serve as a guide to rationalize drug prescribing in older adults by identifying which medications could be discontinued. Secondly, our tool can be used for training purposes for both undergraduate and postgraduate physicians. Training in systematic tools to reduce PIP may result in improved prescribing skills, as already outlined in a prior Dutch randomized controlled trial [52]. Thirdly, it could be an epidemiologic tool; explicit criteria can be used by researchers and health policymakers to investigate the quality of drug use (e.g. trends in prevalence, incidence, patterns, and costs of PIP) and associated outcomes in pharmacoepidemiologic studies conducted in large administrative databases.

Regarding future perspectives, it will be necessary to investigate the clinical relevance of the REMEDI[e]S tool by assessing its ability to prevent serious adverse effects in the older population, as previously performed in other studies [53–56]. Ideally, the inter-rater reliability and the acceptability by healthcare professionals of the REMEDI[e]S tool should be assessed before testing its impact in preventing poor health outcomes [34, 57]. The REMEDI[e]S tool could also be implemented in electronic health records, to promote its use and impact on clinical practice. Indeed, the lack of electronic assessment of PIM lists in electronic health records has been outlined as a barrier to the widespread use of these lists [58]. Moreover, integrating computerized decision support tools in electronic health records may be an effective strategy to reduce inappropriate prescribing by assisting clinicians in their daily clinical practice and training [59, 60]. Also, the development of an electronic version of the REMEDI[e]S tool through a web application is in process. It could help to expand the diffusion of the tool, notably in ambulatory settings, making the tool more recreational and thus facilitating its use in clinical practice.

Conclusion

The REMEDI[e]S tool is an original mixed tool combining both implicit and explicit criteria adapted to French medical practices. It has been devised to provide practical guidance for medication review in order to avoid PIP in older adults aged 75 years and over or 65 years and over with multimorbidity. The REMEDI[e]S tool could be used as a suitable guide to identify and prevent PIP in older people at the individual level in clinical practice and training. It could also be used as an epidemiologic tool to investigate the quality of drug use and associated clinical and economic outcomes in population-based studies, aimed at implementing large targeted-interventions in order to effectively reduce inappropriate prescribing. The current development of this tool as a web application and its possible integration into electronic medical records are ways of both promulgating and integrating of the tool into prescribing practices with the aim of improving the care safety in older adults.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00228-021-03145-6.

Acknowledgements We would like to acknowledge the assistance of Prof Louis Merle, professor emeritus of clinical pharmacology, Faculty of Medicine of Limoges, for his attentive and critical review of the manuscript.

Author contribution BR and MLL conceived and designed the study; BR screened the literature; BR and MLL drafted preliminary criteria; BR conducted the Delphi survey; BR and MLL analyzed the data; JBC, JBB, MCB, JD, JPF, BG, SG, RG, VG, MG, PN, EP, KR, MBVR, and TT participated in the Delphi consensus as experts; BR and MLL interpreted the data. All authors revised the manuscript and approved the final version.

Declarations

Competing interests The authors declare no competing interests.

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