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META-ANALYSIS

Tools and guidelines to assess the appropriateness of medication and aid deprescribing: An umbrella review

Degefaye Zelalem Anlay[1,2] | Kristel Paque[2,3] | Ellen Van Leeuwen[4] | Joachim Cohen[1] | Tinne Dilles[2]

[1]End-of-life Care Research Group, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel and Ghent University, Brussels, Belgium

[2]Centre for Research and Innovation in Care, Nurse and Pharmaceutical Care, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

[3]HAST, Hasselt, Belgium

[4]Clinical Pharmacology Unit, Department of Basic and Applied Medical Sciences & Department of Public Health and Primary Care, Ghent University, Ghent, Belgium

Correspondence
Degefaye Zelalem Anlay, End-of-life Care Research Group, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel and Ghent University, Laarbeeklaan 103, 1090 Brussels, Belgium.
Email: degefaye.zelalem.anlay@vub.be

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Aims: The aim of this umbrella review was to identify tools and guidelines to aid the deprescribing process of potentially inappropriate medications (PIMs), evaluate development and validation methods, and describe evidence levels for medication inclusion.

Methods: Searches were conducted on MEDLINE (Ovid), Embase.com, Cochrane CDSR, CINAHL (EBSCO), Web of Science Core Collection and guideline databases from the date of inception to 7 July 2022. Following the initial search, an additional search was conducted to identify an updated versions of tools on 17 July 2023. We analysed the contents of tools and guidelines.

Results: From 23 systematic reviews and guidelines, we identified 95 tools (72 explicit, 12 mixed and 11 implicit) and nine guidelines. Most tools (83.2%) were developed to use for older persons, including 14 for those with limited life expectancy. Seven tools were for children <18 years (7.37%). Most explicit/mixed tools (78.57%) and all guidelines were validated. We found 484 PIMs and 202 medications with different appropriateness independent of disease for older persons with normal and limited life expectancy, respectively. Only two tools and eight guidelines reported the evidence level, and a quarter of medications had high-quality evidence.

Conclusions: Tools are available for a diversity of populations. There were discrepancies, with the same medication being classified as inappropriate in some tools and appropriate in others, possibly due to low-quality evidence. In particular, tools for patients with limited life expectancy were developed based on very limited evidence, and research to generate this evidence is urgently needed. Our medication lists, along with the level of evidence, could facilitate efforts to strengthen the evidence.

KEYWORDS
elderly, prescribing, systematic review

Degefaye Zelalem Anlay and Kristel Paque are shared first authors. Joachim Cohen and Tinne Dilles are shared last authors.

1 | INTRODUCTION

Deprescribing is a critical aspect of patient care, involving the supervised withdrawal of inappropriate medications by healthcare professionals. It aims to discontinue drugs when potential harms outweigh potential benefits, taking into account individual patient factors such as care goals, functioning, life expectancy, values and preferences.[1]

Recently, deprescribing has gained increased attention, particularly concerning vulnerable populations at higher risk of inappropriate medication use and its consequences. These vulnerable groups include older adults, paediatric patients and individuals with limited life expectancy. The significant increase in the elderly population has led to a rise in comorbidities, which in turn has contributed to an increase in polypharmacy (defined as the use of five or more chronic medications).[2] Being on polypharmacy and age-related changes in drug pharmacodynamics and pharmacokinetics further elevate the risks associated with medication use for older adults.[3,4] This has led to an increased risk of potentially inappropriate medications (PIMs) use, contributing to adverse drug effects, hospitalization,[5] morbidity, mortality[6] and higher healthcare costs.[7] In the case of paediatric patients, unique issues arise due to their rapid growth and developmental changes, which influence how drugs are processed in their bodies.[8] Additionally, individuals with limited life expectancy necessitate a different approach to medication management, emphasizing symptom relief rather than long-term prevention or cure. This emphasis leads to certain medications being potentially inappropriate for individuals with limited life expectancy but appropriate for older persons without such limitations, and vice versa.[9,10]

In response to these challenges, tools and guidelines have been developed to assist clinicians in assessing medication appropriateness, deprescribing PIMs and prescribing suitable medications, particularly for vulnerable populations. These tools and guidelines can either support the overall process of deprescribing (eg, drug-specific deprescribing guidelines) or specific parts of the deprescribing process (eg, tools for identifying PIMs).[11] They can be explicit, providing predefined criteria or lists of medications, or implicit, relying on clinical judgement and expert opinion, or a mix of both explicit and implicit approaches for assessing the appropriateness of medications.[12] Due to cultural, societal and medical differences, a wide range of tools and guidelines has been created to cater to diverse healthcare settings, aiding clinicians in making decisions and increasing their self-efficacy in medication management for improved care for vulnerable groups.[13] Systematic reviews to summarize these tools and guidelines have been conducted at different times.[14]

Nevertheless, despite the importance of a comprehensive evaluation of medication appropriateness using tools and guidelines, only a few systematic reviews have successfully integrated medications from these tools and guidelines.[15–19] These reviews have compiled a list of PIMs for older persons, regardless of their specific disease or condition, and have also considered PIMs interactions with other drugs or diseases. Additionally, they have provided information about therapeutic alternatives and clinical management strategies for identified PIMs reported in publications. However, certain crucial aspects are lacking in these reviews. For instance, they did not compile lists of medications based on their appropriateness for older persons with limited life expectancy. Furthermore, although the compilation of medications lacking consensus among experts regarding appropriateness offers a list of medications warranting further investigation, these reviews failed to provide such list.

Moreover, these reviews did not provide a clear description of the level of evidence supporting each medication included in the tools and guidelines. This limitation underscores the need for more thorough assessments of these tools and guidelines, considering all the aforementioned aspects, to enable informed clinical decision-making. By addressing these gaps, these lists can contribute to the creation of evidence-based medication lists that are widely applicable and can identify areas where further research and evidence are needed and facilitate evidence generation. Therefore, this study aims to achieve the following objectives: (1) identify available tools and guidelines for assessing medication appropriateness and aiding deprescribing of PIMs; (2) evaluate the development and validation methods employed for explicit and mixed tools and guidelines; (3) develop a comprehensive thematic list of medications extracted from identified explicit and mixed tools and guidelines, categorized based on the target populations and rationale for evaluating medication use; and (4) describe the available level of evidence supporting the medications or medication classes included in the identified tools and guidelines.

To achieve the aim of the study, we conducted an umbrella review. While the significant number of systematic reviews lays the foundation for the umbrella review, the limitations of these reviews necessitate a complementary approach, where we utilize them as a steppingstone to access and analyse the tools and guidelines included by these systematic reviews directly, resulting in a more comprehensive and rigorous high-level analysis.

2 | METHODS

This umbrella review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA), and PRISMA for Searching (PRISMA-S),[20] standardized guidelines to ensure quality and clarity.[21] The protocol for this review was developed according to the PRISMA protocol (PRISMA-P) 2015,[22] and registered on PROSPERO, the international prospective register of systematic reviews (CRD42021235348).

2.1 | Eligibility criteria

The eligibility assessment for this study involved a three-stage process. In stage 1, eligible systematic reviews and guidelines were identified. Stage 2 involved the screening of tools to assess the appropriateness of medications and guidelines to aid deprescribing, which were included in the identified systematic reviews. In Stage 3, we selected those tools/guidelines from stage 2 that were

eligible for medication extraction based on the eligibility criteria for Stage 3. The corresponding inclusion and exclusion criteria at each stage are presented in Box 1.

In this study, a distinction was made between "tools" and "guidelines" based on their specific purposes, although these terms are often used interchangeably in the literature. For the purpose of this study, "tools" are defined as resources primarily focused on identifying PIMs. These tools employ a systematic approach or screening mechanism to assess the appropriateness of medications, enabling the identification of medications that may require deprescribing. On the other hand, "guidelines" encompass resources that help clinicians identify and deprescribe PIMs by providing specific advice on when, why and how to stop or taper certain medications.

BOX 1 Eligibility criteria and stages outlined in the study

Inclusion criteria	Exclusion criteria
Stage 1: Identification of systematic reviews and guidelines	
• Peer-reviewed systematic reviews summarizing screening tools for assessment of the appropriateness of medication and/or guidelines in any population	• Systematic reviews describing aspects of use or introduction of tools and guidelines (compliance with the tools and guidelines, the effect of the use of the tools and guidelines, indicators of potentially inappropriate prescribing, prevalence of PIM, associations of PIM with various outcomes, factors influencing PIM use)
• Deprescribing guidelines (reported in accordance with the AGREE-Reporting Checklist[23] or following the GRADE approach[24]) that provide an algorithm or model to stop or taper the dose of a specific PIM	• No language restrictions were applied for full texts, and there were no time or date restrictions. However, systematic reviews and guidelines published in a non-English language without available translation, even after contacting the authors, were excluded
	• No access (ie, when retraction was not possible after trying to contact the authors through ResearchGate, including through email)
Stage 2: Identification of available tools and guidelines included in the systematic reviews	
• Explicit, implicit and mixed tools to assess the appropriateness of medications	• Computerized clinical decision support systems developed based on other tools or general frameworks • Medication review processes without specific drug lists
• Guidelines that support deprescribing on specific medication classes/medications or lists of medications	• No access to the tools and guidelines (unable to retrieve after trying to contact the authors through ResearchGate, including through email, and publications are no longer available online)
Stage 3: Selection of tools and guidelines for extraction of medications	
• Most updated versions of tools (if multiple versions exist)	• Implicit tools, non-validated tools or tools without information about the validation process
• Validated tools and deprescribing guidelines developed based on the GRADE framework	• Translation of original tools without changes in the medication list
	• Tools developed based on other tools without the addition of new drugs or only involving the deletion of medications are excluded. The genealogy of the tools is described based on Ivanova et al[25] to minimize repeated extractions of the same medications and ensure comprehensive coverage of medications

Abbreviation: PIM, potentially inappropriate medication.

2.2 | Data sources and search strategies

The search for relevant studies was conducted in five electronic databases: Medline and PubMed-not-Medline (via Ovid), Embase (via Embase.com), Web of Science (WoS Core Collection, Biosis Citation Index, Chinese Science Citation Database, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Medline, Russian Science Citation Index and SciELO Citation Index), the Cochrane Database of Systematic Reviews (via Cochrane Library) and CINAHL (via EBSCO). The search covered studies from the inception of each database until 7 July 2022. Following the initial search, an additional check was performed to identify updated tools. Five tools that were updated in late 2022 and 2023 (until 17 July 2023) were identified and included in the updated versions of the tool lists and medication lists.

In addition to the article databases, five guideline databases were searched for relevant deprescribing guidelines: Guidelines International Network (G-I-N), Scottish Intercollegiate Guidelines Network (SIGN), Guideline Central, Trip Guidelines and Richtlijnen databank (the Dutch guideline database). The Bruyère Research Institute website was also checked for any additional deprescribing guidelines.[26] Furthermore, a backward snowballing approach was employed by manually screening the bibliographic lists of the included systematic reviews to identify additional relevant studies.

The search strategy utilized a combination of controlled vocabulary and free text words related to the concepts of inappropriate/appropriate medication, systematic reviews and guidelines. These terms were applied to titles, abstracts and author keywords to ensure a comprehensive search within these concepts. To maintain the quality of the search strategies, a medical librarian (K.T.) was involved in developing and evaluating the search strings. For a more detailed description of the databases searched and the specific terms used in the search strategy, refer to the additional details provided in Supporting Information Data S1.

2.3 | Data collection and analysis

2.3.1 | Selection of studies

The references identified through the search were imported into EndNote X9 reference management software (Clarivate) and deduplicated. After removing the duplicates, the references were exported to Rayyan's free web application to facilitate the selection process.[27] In the first phase, studies were included for full-text review if the abstract was in English and the study design was clearly stated in the title and/or abstract as a systematic review or guideline. Articles or guidelines included for full-text review were also independently reviewed by K.P. and D.Z.A. as a second stage of screening. Conflicts throughout the selection process were first discussed by the two independent reviewers until consensus was reached. When consensus could not be reached, the research team was involved in the discussion.

2.3.2 | Assessment of risk of bias in included systematic reviews

The assessments of the quality of eligible studies were conducted by two independent reviewers (D.Z.A. and K.P.) using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Systematic Reviews.[28] This checklist contains 11 questions that assess specific domains of the systematic reviews to determine the potential risk of bias and could be answered "yes", "no", "unclear" or "not applicable". Any disagreement in scoring was resolved by discussion and further discussion in the research group to reach a consensus. We calculated the final score by adding up all "yes" responses and dividing this sum of scores by the number of items scored (11). The risk of bias in individual systematic reviews was determined using the following cutoffs: low risk of bias if the final score was ≥70%, moderate risk if the score was 50-69% and high risk of bias if the score was below 50%. For the included guidelines, the quality assessment was conducted using the Appraisal of Guidelines for Research and Evaluation II (AGREE II), consisting of 23 items within six quality domains. Each item was rated on a seven-point scale (from a score of 1 for "strongly disagree" to a score of 7 for "strongly agree").[29] The individual reviewer scores of all 23 items were summed for each study, and the average total score of two reviewers was obtained to derive the scaled all-domain score percentage. The quality of the study was classified based on the scaled all-domain score (high ≥70%, moderate 50-69% and low <50%).

2.3.3 | Data extraction and management

The data were extracted in three stepwise procedures. First, we focused on the characteristics of the included systematic reviews and guidelines. Next, we examined the characteristics of tools and guidelines identified in the included systematic reviews. Finally, we collected information about the medications within the selected tools and guidelines for medication extraction. To ensure consistency and accuracy, we utilized a self-developed data extraction form, which underwent piloting and discussion among the authors. This process aimed to prevent the omission of important data and to ensure that all reviewers obtained comparable results. During the data extraction, one reviewer (D.Z.A.) was responsible for gathering data on various aspects, such as the objective of the systematic review and guidelines, the databases searched, the number of included tools and guidelines in the systematic review, the nature of tools in the included systematic review, the eligibility criteria for the systematic review, the name of the tool and guidelines, the country where the tool was developed, the setting/context, target populations, aspects of inappropriateness or deprescribing covered by the tool and guidelines, the content of the tool and guidelines, and the development and validation technique of tools. To maintain quality, a second reviewer (K.P.) crosschecked all the extracted data. In addition to the above, two reviewers (G.V. and D.Z.A.) independently collected data on outcomes related to medications. This included the Anatomical Therapeutic Chemical (ATC) class of each medication and the grading of recommendations if reported in

the included explicit tools and guidelines. Any discrepancies that arose between the reviewers were thoroughly discussed within the review team until a consensus was reached.

2.3.4 | Data synthesis and compilation of drug lists

Data on complete lists of medications, characteristics of tools, development methods, validation methods and aspects of inappropriate prescribing covered by tools were entered into Excel. Individual medications/medication classes reported in the tools and guidelines were also entered into Excel and grouped into ATC classes.[30]

Separate lists of medications were developed according to the target populations covered, such as paediatric patients, older persons with normal life expectancy (≥65 years) and older persons with limited life expectancy (≥65 years). Limited life expectancy is defined throughout this document as an umbrella term representing frailty, advanced diseases and end-of-life care situations. This definition also includes tools intended for frail older persons with limited life expectancy but that do not provide frailty criteria or specify the duration of remaining life.

The medication/medication classes for each target population were categorized based on aspects of the appropriateness of medications (PIM independent of disease/condition, PIM dependent on specific diseases, drug-drug interactions, drug-dose adjustments, medications questionable benefits, drugs to be used with caution, potentially inappropriate omissions, paediatric potentially inappropriate prescriptions, fall risk drugs, paediatric PIM lists, among others). For this review, drugs with questionable benefit are defined as medications for which the expert group did not reach a consensus on whether a specific medication is PIM or not. A separate description of the methodology used to develop these lists, considering each aspect of the appropriateness of medications, can be found in Supporting Information Data S2.

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[31–33]

3 | RESULTS

3.1 | Study selection and quality assessment

A comprehensive search strategy yielded 20 955 records from various databases and sources. After removing duplicates, 10 606 records underwent screening based on title and abstract, resulting in 66 records that were assessed in full-text form. A manual search of reference lists did not yield any additional relevant publications. Ultimately, 23 records, including 15 systematic reviews[12,14–19,34–41] and eight guidelines,[42–49] were included in this review (Figure 1). The detailed characteristics of these systematic reviews and guidelines can be found in Tables 1 and 2, respectively. The reasons for excluding records during full-text reading are provided in Supporting Information Data S3.

The quality assessment of the included studies revealed that 11 systematic reviews demonstrated a low risk of bias,[12,15,17–19,35,36,38–41] while the remaining reviews exhibited a moderate[14,16] or high risk of bias.[34,37] Among the guidelines, 7 (77.8%) were considered of high quality in terms of their development,[42–45,47,49,52] while 2 (22.2%) were rated as moderate quality.[48,50] Four guidelines fully met all items of the AGREE-II assessment tool, further supporting their high quality.[43,45,49,52] Additional information justifying the assessments of bias can be found in Data S4.

3.2 | Available tools and guidelines for assessing medication appropriateness and aiding in deprescribing PIMs

In our study, we initially identified 356 tools and 32 guidelines from the included systematic reviews. After removing duplicate tools and guidelines published in multiple reviews and conducting eligibility evaluations, we narrowed down our selection to 95 unique tools and nine guidelines that were relevant to our study. The flow diagrams presented in Figure 2 illustrate the application of each stage of eligibility assessment and the corresponding results throughout the three stages. For detailed characteristics of the identified tools, see Table 3. Additional information regarding the exclusion of tools and guidelines at different stages of eligibility assessment can be found in Supporting Information Data S3.

3.2.1 | Nature of tools

The majority of the tools included in the review were developed in Europe ($n = 45/95$, 47.37%) and the United States ($n = 26/95$, 27.37%), while most of the available deprescribing guidelines were developed in Canada ($n = 6/9$, 66.7%). In terms of the nature of the tools, most were explicit tools ($n = 72/95$, 75.78%), 11 (11.57%) were implicit tools with scoring systems and the remaining 12 (12.63%) were mixed tools. Out of the identified tools, we found that only nine (9.5%) explicit tools have been updated at least once.[56–60,62–66] This includes tools like the Beers criteria, which undergo regular updates, and PRISCUS 2.0,[60] which has been updated once.

3.2.2 | Target populations

The target populations for the tools varied in terms of age groups, settings and applicability for patients with limited life expectancy. The majority of the tools were developed for adults aged 65 years and older

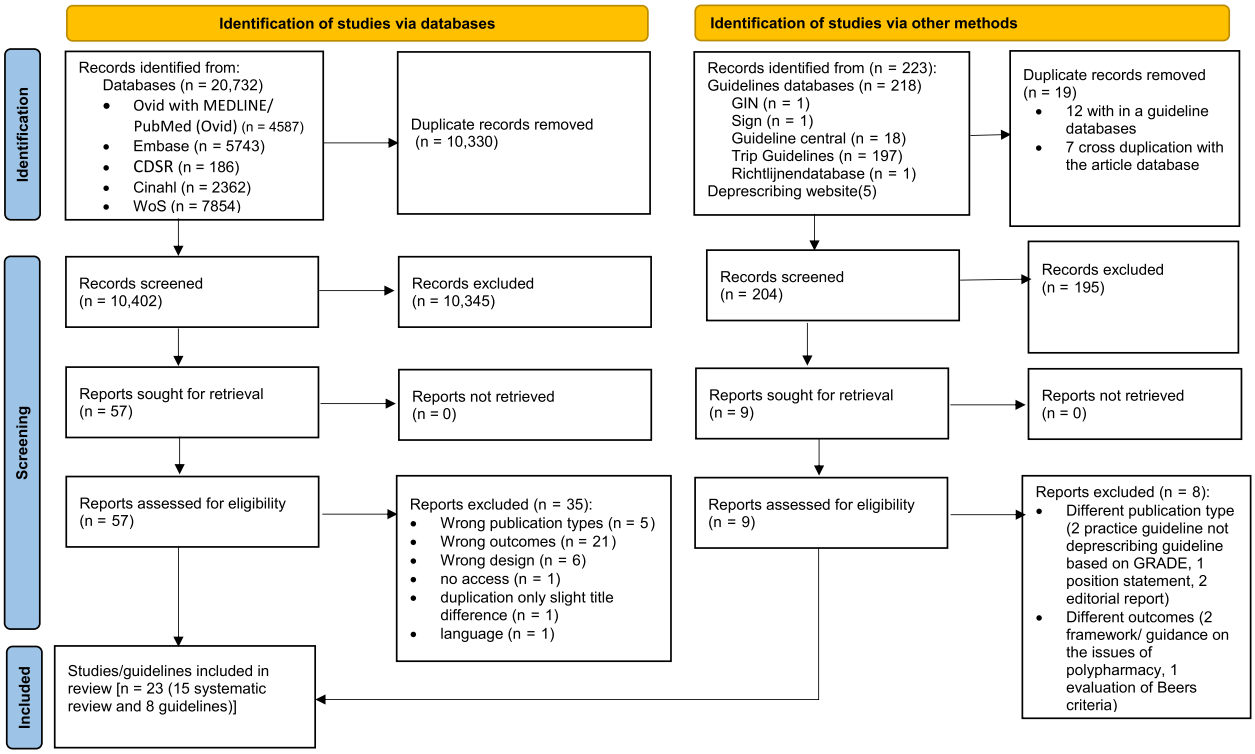

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses 2020 (PRISMA 2020) flow diagram for the study selection process in the umbrella review, 2023. CDSR, Cochrane Database of Systematic Reviews; CINAHL, Cumulative Index to Nursing and Allied Health Literature; GIN, Guideline International Network; SIGN, Scottish Intercollegiate Guidelines Network; WoS, Web of Science.

($n = 79/95$, 83.16%), recognizing the unique medication management needs of this population. There were also a small number of tools specifically designed for paediatric patients ($n = 7/95$, 7.37%).[63,67–73] Additionally, there were tools intended for other age groups or that did not specify a particular age group ($n = 9/95$, 9.47%).[74–82]

The identified tools can also be categorized based on their applicable settings. First, there are tools that can be utilized across all healthcare settings ($n = 18/95$, 18.94%),[62,63,68–71,83–94] including primary care, long-term care and secondary care, providing a comprehensive approach to deprescribing. Second, some tools are specifically designed for all healthcare settings except hospice and palliative care ($n = 5/95$, 5.26%),[58,66,95–97] making them suitable for primary care and secondary care but not specifically tailored for end-of-life care. Third, there are tools specifically tailored for long-term care facilities or nursing homes ($n = 10/95$, 10.52%),[77,79,98–105] that address the unique medication management needs of older adults residing in these settings. Additionally, there are tools that focus on the community setting ($n = 19/95$, 20%),[64,67,73,82,106–118] targeted to aid deprescribing in primary care clinics, ambulatory centres and outpatient facilities. Lastly, there are tools specifically aimed at secondary care settings ($n = 8/95$, 8.42%),[74,75,78,80,81,119–121] providing guidance for deprescribing in hospital inpatient settings and specialized care delivered by medical specialists. It is worth noting that a subset of tools ($n = 35/95$, 36.84%) does not specify a particular setting, indicating their potential applicability across various healthcare contexts.[56,57,59,60,65,75,76,122–149]

Furthermore, a subset of the identified deprescribing tools and guidelines (14 tools and five guidelines) has been specifically developed to assess the appropriateness of medication use for older adults with limited life expectancy. These tools cater to the unique needs of older adults facing limited life expectancy, including advanced dementia,[52,101,125] advanced cancer,[80,81] frailty and/or varying durations of remaining life expectancy.[43,44,48,50,62,91,102–105,119,123,150]

3.3 | Tools and guidelines development approach

The development process of the tools and guidelines exhibited significant variability in terms of approach, content and the aspects of medication inappropriateness they addressed, including PIMs both independent of and dependent on specific diseases/syndromes, as well as drug-drug interactions (Table 3). The contents of these tools were also influenced by the availability of medications in the countries where they were developed, and in some instances they were tailored based on the prevalence of certain diseases in the country.[59,62,63] Notably, a majority of the guidelines (eight out of nine, which accounts for 88.9%) focused on providing recommendations specifically for certain drug classes. These classes included antihyperglycaemic medications,[43,50] proton pump inhibitors,[44,49] psychotropic drugs,[42,47,52] benzodiazepine receptor agonists,[45] statins and medications for antihypertensive therapy and antiplatelet use[44] (Table 2).

TABLE 1 Summary of included systematic reviews listing tools to assess the appropriateness of medications.

Reference	Objectives	Inclusion criteria	Exclusion criteria	Searched databases	Search period
Aguiar et al[15]	Identify PIMs with risk of cardiovascular adverse events from lists already published in the literature	Articles describing PIM lists that included individuals aged 65 or older and objectively presented PIMs to be avoided by the elderly and drug-disease interactions with risk of CVS adverse events	Articles describing PIMs without any association with ADRs. Non-English and/or unavailable full-text articles	PubMed, Ovid® MEDLINE, Google Scholar, manual search	1 January 1991 to 11 September 2017
Darr-Foit et al[34]	Addresses the concept of "deprescribing" in the context of recommendations for use of systemic drugs contained in current dermatological guidelines	Not clear (limited to all guidelines for which the German Dermatological Society was responsible)	Not clear (under revision or did not propose systemic medication)	Online portal of the Association of the Scientific Medical Societies	
Dimitrow et al[35]	Review existing criteria that measure inappropriate prescribing in individuals aged 65 and older and to define the circumstances of their use (explicit/implicit), origins, development processes and content	Original articles describing criteria of measuring in appropriate prescribing written in English were included if they described the development of the criteria	Articles that described criteria applicable only in hospital settings, specific drugs or a particular disease or condition were excluded. Articles assessing the quality of prescribing or medication use at the healthcare level were also excluded	MEDLINE (Ovid) and PubMed manual search	1 January 1990 to 17 July 2010
Farhat et al[14]	Review of systematic reviews listing explicit tools developed to detect prescribing errors and to assess the impact of explicit tools on clinical and economic outcomes	Systematic reviews listing explicit tools, dedicated to geriatrics or internal medicine populations Any clinical setting was considered (eg, hospital and nursing home). No restriction was imposed on the type of health centres	RCT targeted the frail, paediatric or specific populations, RCT applied other than an explicit tool	PubMed	September 1991 to 30 September 2020
Kaufmann et al[12]	To create a comprehensive and structured overview of existing tools to assess inappropriate prescribing	Tools or computerized decision support systems to assess inappropriate prescribing, updated versions of already published tools and adaptations of an already published tool if its further development was based on new expert consensus. Studies report tools specifically in adults and published in English or German	Tools restricted to specific therapeutic classes or specific diseases, tools targeted to children, adaption of already published tools to computerized decision support systems, medication review techniques which did not use a tool, educational interventions to improve prescribing practice, validation studies of previously published tools and general guidelines or recommendations	Pubmed	1 January 1991 to 19 March 2013

(Continues)

TABLE 1 (Continued)

Reference	Objectives	Inclusion criteria	Exclusion criteria	Searched databases	Search period
			to assess inappropriate prescribing		
Lee et al[17]	To determine the similarity of PIM specified in and between existing explicit lists and the availability in Australia of medications included on existing lists to determine their applicability to the Australian context	Explicit lists of PIMs for older adults, the most recent version and having the complete list published in English were included. Lists modified and adapted from another list for a different clinical population or geographical location were included	Published lists based on an existing list if no changes were made from the original list or if the new list consisted only of deletions, simplifications or rephrasing of the previous list, implicit tools	Ovid EMBASE Ovid MEDLINE and Elsevier Scopus, manually review of list of articles published in the previous seven systematic reviews	EMBASE (1974-April 2021), MEDLINE (1946-April 2021) and Elsevier Scopus (2004-April 2021)
Lucchetti et al[16]	To review all PIMs for older persons included in prescribing criteria published in the last decade	Articles describing the development of criteria for PIM use in older adults. Latest version of the tool	Articles not addressing the target topic, investigating the use of these criteria in clinical and non-clinical settings, theoretical reviews of inappropriate prescribing, duplicate publications, prescription omission criteria (ie, START) and criteria for institutionalized or hospitalized patients	PubMed and Medline	1 January 2006 to 31 December 2015
Masnoon et al[36]	To summarize available prescribing appropriateness assessment tools and criteria, and their associations with patient-related outcomes	Studies in English that were already published or in press	NS	MEDLINE, EMBASE and Informit (Health Collection)	2000 to 2016
Motter et al[18]	To summarize and compare validated PIM lists for older peoples published in different countries between 1991 and 2017	Original studies describing the explicit criteria used to determine PIMs, describe the development and validate the methods used in the PIM list. Interventions and observational studies that evaluated PIMs were also retained	Medication review techniques using implicit criteria to evaluate PIMs and lists of PIMs restricted to specific therapeutic classes or specific diseases, 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	PUBMED, AgeLine, Academic Search, Academic Search Premier and CINAHL	January 1991 and April 2017
Renn et al[37]	Examined published practice recommendations for discontinuation of ChEIs in AD	Guidelines that addressed patient care or treatment recommendations for dementia broadly or AD specifically. Five pertinent medical textbooks in the	Exclusively pertained to a disorder other than AD, specific pharmacological treatments other than cholinesterase inhibitors, specific aspects of patient care or to a non-	PubMed Guidelines databases Seven relevant professional societies Google search engine	Since 2005

TABLE 1 (Continued)

Reference	Objectives	Inclusion criteria	Exclusion criteria	Searched databases	Search period
		disciplines (neurology, geriatrics, psychiatry, medicine, pharmacology) and one specialty topic (dementia) reviewing diagnosis, treatment and practice in the relevant subspecialty	prescribing discipline, unrelated aspect of medicine or practice (eg, nursing guides, paediatric psychiatry)		
Schiavo et al[19]	Identify explicit screening tools used to identify PIMs on older people, and identify the PIMs, PIMs interactions (PIMs-drugs and PIMs-diseases), therapeutic alternatives and clinical management for PIMs reported in publications and in these explicit screening tools used to identify PIMs	Studies that developed and/or validated explicit screening tools to identify and report PIMs for older people; PIMs interactions (PIMs-drugs and PIMs-diseases) and/or suggested strategies for clinical management and/or the use of therapeutic alternatives. The most recent versions of the tool were included	Editorials, commentaries, letters, reviews, news reports, abstracts from conference proceedings, theses and dissertations were excluded. Studies written in non-Roman alphabet languages (eg, Russian, Japanese and Chinese)	PubMed and Scopus Records identified from reference of articles	Inception until May 2021
Systematic reviews included tools used for paediatric age groups					
Li et al[38]	To systematically evaluate children's PIP screening tools and validation studies on these tools	PIP screening tools for children, validation studies on PIP screening tools, described as a clinical study which aims to assess the feasibility or reliability of PIP screening tools	Repeated publication, review, unobtainable full texts, not the latest version, non-Chinese and non-English	PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), Chinese scientific Journals Database (CSJD-VIP) and Wanfang Data	Not provided (retrieval before May 2021)
Corrick et al[39]	Identify and provide an overview of all paediatric rational prescribing tools	Articles describing tools targeted at evaluating the rationality or appropriateness of prescriptions, updated and revised versions of previously published tools, including tools limited to specific drugs, drug groups, diseases or disease groups	Tools targeting adults and not specified target patient groups, indicators that assess rates or percentages of prescription types, validation study of a previously published tool, educational interventions aimed at improving prescribing, and guidelines describing recommended prescribing	Ovid MEDLINE, Embase, International Pharmaceutical Abstracts and CINAHL	Inception untill July 2019
Systematic reviews covered tools used to apply for patients with limited life expectancy					
Thompson et al[40]	To summarize available tools that can assist clinicians in identifying and reducing or stopping (deprescribing) PIMs	Studies had to state explicitly that the tool was designed for this population or include specific considerations relevant to this population	Aimed exclusively at individuals with cancer in the palliative care setting	MEDLINE (via Ovid SP), EMBASE (via Ovid SP) and CINAHL, along with grey literature	Inception to December 2017

(Continues)

TABLE 1 (Continued)

Reference	Objectives	Inclusion criteria	Exclusion criteria	Searched databases	Search period
	and that specifically consider frailty or LLE				
van Merendonk et al[41]	Summarize and compare available guidelines and tools to deprescribe for palliative cancer patients	Studies included palliative cancer patients. Applying a tool or certain criteria for screening of medications were included if they were applied to palliative cancer patients. Only electronic articles available in English were included	Studies focusing on a population without palliative cancer patients, studies not applying a tool or guideline, studies focusing on one specific medication category	SCOPUS and PubMed	Carried out a literature search in December 2020

Abbreviations: AD, Alzheimer's disease; ADR, adverse drug reaction; ChEI, cholinesterase inhibitor; CVS, Cardiovascular system; JBI, Joanna Briggs Institute; LLE, limited life expectancy; NS, not specified; PIM, potentially inappropriate medications; PIP, potentially inappropriate prescription; RCT, Randomised Clinical Trial.

TABLE 1 (Continued)

Reference	Objectives	Inclusion criteria	Exclusion criteria	Searched databases	Search period

[a]Both tools and guidelines aid the deprescribing process. Tools are used to identify PIMs. These PIM tools can be explicit (ie, criteria based, providing a list of drugs as potentially inappropriate or as candidates for deprescribing), implicit (ie, describing appropriateness based on users' clinical judgement) or mixed tools that combine both. Guidelines help clinicians to identify PIMs as well as provide specific guidance on how to deprescribe these medications.

TABLE 1 (Continued)

Reference	Included population	Types of included study	Tool type[a]	Number of studies	Number of tools	JBI score (11)
Aguiar et al[15]	65+ years	Original articles, reviews, systematic reviews	Explicit and mixed	24	19 lists and five updates	11
Darr-Foit et al[34]		Dermatology guideline	Guideline		16	3
Dimitrow et al[35]	65+ years	Original articles	Implicit and explicit	16	14 (10 explicit, three implicit and one mixed)	8
Farhat et al[14]	65+ years	Systematic review	Explicit	3	49 explicit tools	7
Kaufmann et al[12]	Adults		Implicit, explicit and mixed	46	46 (28 explicit, eight implicit, 10 mixed)	9
Lee et al[17]	Older adults	Original research	Explicit	35	35	11
Lucchetti et al[16]	Older adults		Explicit	14	14	6
Masnoon et al[36]	Any age	Any study design	Implicit and explicit	42	42, 26 (explicit)	10

TABLE 1 (Continued)

Reference	Included population	Types of included study	Tool type[a]	Number of studies	Number of tools	JBI score (11)
Motter et al[18]	65+ years	Original studies	Explicit	36	36	11
Renn et al[37]	Not specified	Practice guideline,[16] and textbook[39]	Guideline and textbooks on discontinuation	16	ChEI	5
Schiavo et al[19]	60+ years	Clinical trials, observational studies and studies conducted by a panel of experts	Explicit tools	58	614 PIMs and 747 PIMs interactions	8
Systematic reviews included tools used for paediatric age groups						
Li et al[38]	Children (0-18 years)	Original and validation study of the tools	Explicit	9	5 (screening tool) and 4 (validation study)	11
Corrick et al[39]	<18 years		Explicit and mixed	5	3	9
Systematic reviews covered tools used to apply for patients with limited life expectancy						
Thompson et al[40]	Frail older persons and older persons with LLE		Models/frameworks of deprescribing[2] Entire medication list approach[9] Medication specific approach[4]	15	15	10
van Merendonk et al[41]	Palliative cancer patients		Implicit, explicit, guidelines	9	9	8

Abbreviations: AD, Alzheimer's disease; ADR, adverse drug reaction; ChEI, cholinesterase inhibitor; CVS, Cardiovascular system; JBI, Joanna Briggs Institute; LLE, limited life expectancy; NS, not specified; PIM, potentially inappropriate medications; PIP, potentially inappropriate prescription; RCT, Randomised Clinical Trial.

[a]Both tools and guidelines aid the deprescribing process. Tools are used to identify PIMs. These PIM tools can be explicit (ie, criteria based, providing a list of drugs as potentially inappropriate or as candidates for deprescribing), implicit (ie, describing appropriateness based on users' clinical judgement) or mixed tools that combine both. Guidelines help clinicians to identify PIMs as well as provide specific guidance on how to deprescribe these medications.

TABLE 2 Summary of guidelines to support deprescribing of potentially inappropriate medications.

Reference (country, year)	Objectives	Evidence for the guideline development	Approach of the guideline development
Bjerre et al[42] (Canada, 2018)	To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper and stop antipsychotics	Systematic review of clinical trial, review of review	GRADE
Farrell et al[49] (Canada, 2017)	To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper or stop PPIs	Systematic review of PPI deprescribing, reviews of the harm of continued PPI use, syntheses of patient preferences and resource implications	GRADE
Pottie et al[45] (Canada, 2018)	Develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper and stop BZRA	Scoping review followed by systematic review	GRADE
Department of Health[47] (Irish guideline, 2019)	To provide clear and evidence-based recommendations on appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia	Systematic review of studies and guidelines	GRADE approach/evaluate by AGREE II
Guidelines consider frail elderly and/limited life expectancy			
Kojima et al[48] (Japan, 2016)	Update the list of PIMs extracted from *Guidelines for medical treatment and its safety in the elderly 2005* based on the recently published *Guidance statement on appropriate medical services for the elderly*	Systematic review of 15 diseases, conditions and special areas pertinent to clinical care	GRADE
Farrell et al[43] (Canada, 2017)	To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper, stop or switch antihyperglycaemic agents in older adults	Systematic review	GRADE
Mallery et al[50] (Canada, 2013)	Develop and disseminate guidelines for the treatment of frail older adults with type 2 diabetes	Literature (meta-analysis, review of trials)	AGREE reporting approach
Reeve et al[51] (Canada and Australia, 2018)	To develop an evidence-based clinical practice guideline for deprescribing ChEIs and memantine, using robust international guideline development processes	Systematic review and expert opinion and non-systematically reviewed evidence	GRADE
Onder et al[44] (Italy, 2022)	To develop recommendations for the clinical management of persons with multimorbidity and/or polypharmacy and to provide evidence-based guidance to improve their quality of care	Review of literature (article databases and NICE)	GRADE

Abbreviations: AD, Alzheimer's disease; AGREE II, Appraisal of Guidelines for Research and Evaluation II ; BZRA, benzodiazepine receptor agonists; CBT, cognitive behavioural therapy; ChEI, cholinesterase inhibitors; GDT, guideline development team; GP, general practitioner; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; H2RA, histamine-2 receptor antagonist; HbA1c, Hemoglobin A1c; LLE, limited life expectancy; PIM, potentially inappropriate medications; PPI, proton pump inhibitor.

[a]The wording of the final recommendations in the GRADE frameworks of the three guidelines was based on the cut-off ≥80% of the GDT agreement, but the Irish guideline did not specify the cut-off for guideline development group consensus.

[b]Trial deprescribing (slowly reducing the medication dose [tapering] prior to complete cessation, with monitoring throughout the process).

TABLE 2 (Continued)

Reference (country, year)	Content[a]	Target population: to whom the guideline applies	AGREE II quality (score)	Setting/audience
Bjerre et al[42] (Canada, 2018)	Recommendations on disease-specific medication classes (antipsychotics) on how to stop the medication with tapering and without tapering. The cut-off for consensus of the final recommendations wording was based on ≥80% of GDT agreement. The GDT comprised 10 members (nine clinicians [four pharmacists, two geriatricians, two family physicians, one geriatric psychiatrist] and one Cochrane methodologist)	Adults, including elderly, who have been prescribed antipsychotics for insomnia or for behavioural and psychological symptoms of dementia. Behavioural and psychological symptoms of dementia treated for >3 months' symptom control or no response to therapy and primary insomnia treated with any duration where underlying comorbidities are managed	High (94.5%)	Canadian primary care and long-term care physicians, pharmacists, nurse practitioners, and specialists who care for patients taking antipsychotics
Farrell et al[49] (Canada, 2017)	Recommendations on disease-specific medication/medication classes (PPIs) on stopping (abrupt or tapering), stepping down (abrupt or tapering followed by prescription of H2 RA) and reducing the dose (on-demand or intermittent, lower dose use). The cut-off for consensus of the final recommendations wording was based on ≥80% of GDT agreement. The GDT comprised 10 members (five voting [one family physician, three pharmacists and one gastroenterologist] and five non-voting members for the final recommendations)	18+ years (including the elderly) taking a continuous PPI for longer than 28 days for the purpose of treating gastroesophageal reflux disease or esophagitis	High (98.9%)	Primary-care physicians, pharmacists, nurse practitioners and specialists who care for patients who might use PPIs
Pottie et al[45] (Canada, 2018)	Recommendation on disease-specific medication classes/medications (BZRA) on stopping, tapering dose, CBT, combining tapering and CBT, reducing BZRA use, providing substitutive therapy. The cut-off for consensus of the final recommendations wording was based on ≥80% of GDT agreement. The GDT comprised nine members [eight clinicians (one family physician, two psychiatrists, one clinical psychologist, one clinical pharmacologist, two clinical pharmacists and one geriatrician) and a methodologist]	Primary insomnia or comorbid insomnia (adults aged 18 to 64 years who take BZRAs for most days of the week for more than 4 weeks, and elderly adults 65+ years regardless of duration)	High (98.9%)	Primary-care physicians, pharmacists, nurse practitioners or other specialists who care for patients taking BZRAs for insomnia
Department of Health[47] (Irish guideline, 2019)	Recommendations on disease-specific psychotropic medication classes/ medications (antipsychotics, ChEIs and memantine, antidepressants, anticonvulsants, Z-drugs and melatonin) on appropriate versus non-appropriate use. Each recommendation was assigned a grade	All adults (18 years and older) with a diagnosis of dementia, of any type with non-cognitive symptoms	High (90.3%)	For all settings that provide care for an adult with dementia doctors, nurses, pharmacists and health and social care professionals

(Continues)

TABLE 2 (Continued)

Reference (country, year)	Content[a]	Target population: to whom the guideline applies	AGREE II quality (score)	Setting/audience
	for quality of evidence and strength of recommendation by the guideline development group (32-person multidisciplinary team) and decision was reached based on consensus			
Guidelines consider frail elderly and/limited life expectancy				
Kojima et al[48] (Japan, 2016)	Non-disease-specific list of medication classes/medications (Included 29 medications that could only be prescribed with special cautions and accompanying flow charts for deprescribing or cautious initation when better alternative medications are lacking. It also includes 8 medications consider for initiation and also accompanying flow charts to start). For each list the quality of evidence and strength of recommendation was assigned based on the literature and voted consensus by the multidisciplinary authors (no specific GDT assigned). No specific cut-off point was provided to define consensus	List of drugs to be prescribed with special caution for those aged 75+ years or frail elderly <75 years or in need of special care. List of drugs to consider starting is oriented to elderly individuals of all ages	High (75.3%)	GPs on the frontline, pharmacists and nurses involved in pharmacotherapy
Farrell et al[43] (Canada, 2017)	Recommendations on disease-specific medication/medication classes (antihyperglycaemic medications with or without hypoglycaemic risk) on when and how to stop the medication, dose reduction or prescription substitution. The cut-off for consensus of the final recommendations wording was based on ≥80% of GDT agreement. The GDT comprised nine members [seven clinicians (two family physicians, three pharmacists, one nurse practitioner, one endocrinologist), one clinical epidemiologist, one not provided]. All clinician members were expert in type 2 diabetes management in older people	65+ years receiving at least one antihyperglycaemic medication to treat type 2 diabetes and who are at risk of hypoglycaemia, at risk of other antihyperglycaemic adverse effects or for whom benefit is uncertain owing to frailty, dementia or LLE	High (98.9%)	Physicians, pharmacists, nurse practitioners, registered nurses and certified diabetes educators caring for older adults with type 2 diabetes who are receiving the medications
Mallery et al[50] (Canada, 2013)	Recommendations on disease-specific medication/medication classes (antihyperglycaemic medications) for actions based on glycaemic level. Decrease or discontinue diabetes treatment (HbA1c <8%). Consider increasing diabetes treatment (HbA1c >12%): unnecessary to	Frail older adults (65 years and above) with type 2 diabetes	Moderate (62%)	Nursing home settings. Continuing education needs of healthcare professionals

TABLE 2 (Continued)

Reference (country, year)	Content[a]	Target population: to whom the guideline applies	AGREE II quality (score)	Setting/audience
	alter therapy if an individual with LLE has tolerated at high HbA1c level (not experiencing hyperglycaemic-associated symptoms). The guideline committee involves an endocrinologist, a geriatrician, a family physician/medical director of a long-term care facility, long-term care nurses, nutrition staff, diabetes educators and a representative from the Department of Health Continuing Care Branch. Each recommendation is accepted based on agreement of all committees			
Reeve et al[51] (Canada and Australia, 2018)	Recommendations on disease-specific medication/medication classes: ChEI (donepezil, rivastigmine, galantamine), memantine on discontinuation or trial deprescribing approach.[b] The cut-off for consensus of the final recommendations wording is based on ≥80% of GDT agreement. The GDT comprises 12 members (10 clinicians: geriatrician/clinical pharmacologist, geriatric psychiatrist, GP, GPs with aged-care accreditation, registered nurse and pharmacists) and two consumer representatives (a person with mild dementia and a carer of a person with dementia)	Adults with AD or dementia of Parkinson's disease, Lewy body dementia or vascular dementia taking medications for more than 12 months, who do not have appropriate indication, never benefited or appear to be no longer benefitting, and those with severe or end-stage dementia	High (100%)	Clinicians involved in the care of adults prescribing a ChEI or memantine, including but not limited to GP, specialist physicians, nurses and pharmacists
Onder et al[44] (Italy, 2022)	Recommendations on management of multimorbidity and/or polypharmacy, including specific medication/medication classes (antihypertensive, PPI, statin and aspirin, including other antiplatelet). No recommendations on discontinuation of antihypertensive therapy and antiplatelet, including aspirin, related to poor quality of evidence. Provide recommendations on deprescription and possible reintroduction of PPI, discontinuation of statin therapy for all with <1 year life expectancy and risk-benefit analysis for age 80+. The recommendations were developed based on the consensus of the expert panels. The guideline development panel involved	Persons with multimorbidity and/or polypharmacy as well as the prioritization of care through the identification of persons at increased risk of negative health outcomes	High (92.2%)	Persons with multimorbidity and/or polypharmacy and their caregivers, healthcare professionals and the healthcare system

(Continues)

TABLE 2 (Continued)

Reference (country, year)	Content[a]	Target population: to whom the guideline applies	AGREE II quality (score)	Setting/audience
	scientific societies operating in the fields of geriatrics, internal medicine, pharmacology and general medicine, and from multidisciplinary fields (epidemiologists, pharmacists, internists, geriatricians, pharmacologists, GP and nurses, and a patient advocate)			

Abbreviations: AD, Alzheimer's disease; AGREE II, Appraisal of Guidelines for Research and Evaluation II ; BZRA, benzodiazepine receptor agonists; CBT, cognitive behavioural therapy; ChEI, cholinesterase inhibitors; GDT, guideline development team; GP, general practitioner; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; H2RA, histamine-2 receptor antagonist; HbA1c, Hemoglobin A1c; LLE, limited life expectancy; PIM, potentially inappropriate medications; PPI, proton pump inhibitor.

[a]The wording of the final recommendations in the GRADE frameworks of the three guidelines was based on the cut-off ≥80% of the GDT agreement, but the Irish guideline did not specify the cut-off for guideline development group consensus.

[b]Trial deprescribing (slowly reducing the medication dose [tapering] prior to complete cessation, with monitoring throughout the process).

The development followed a diverse approach, categorized into six distinct methodologies, reflecting the various techniques used by researchers and healthcare experts.

1. *Systematic (literature) review-based tool development*: The review was utilized by tool developer in four ways. First, researchers employed a systematic review to develop tools solely based on existing tools, using them as the primary foundation for creating new tools. Approximately 42.8% ($n = 36/84$) of explicit/mixed tools were developed based on existing tools. Second, they conducted systematic literature reviews to gather insights from existing tools and guidelines, and then enriched these tools with new evidence or knowledge. Third, they engaged in comprehensive literature reviews to establish a solid foundation for tools, refining them with the incorporation of new evidence and clinical experience. Lastly, they conducted systematic literature reviews of original articles to create entirely new tools.[15,43,44,48,50,52,56–60,63–71,73,81–83,85,89,90,92,94–99,108,110,111,113–115,119,122–124,126,130,133,136,137,139,140,142,144,146–149,151,152]
2. *Adaptation from existing tools*: We found 13 tools and guidelines following this approach,[80,84,88,100,102,103,106,109,127,131,141,145,153] which involved tailoring existing tools to specific contexts and patient groups. For instance, tools were adapted from criteria such as the Beers criteria,[106,109,141,145] STOPP-START[84,88,131] and EU (7)-PIM list,[127,153] for use in different countries, to suit frail elderly in nursing home settings or study purposes.
3. *Reclassification of existing tools*: This approach involved rearranging or redefining criteria in pre-existing tools to address medication appropriateness issues more effectively. For instance, the Fit fOR The Aged (FORTA) list was originally proposed as a reclassification of the Beers criteria, providing both positive and negative lists based on the indications to better suit the target population. Additionally, FORTA lists were assessed for possible reclassification based on updated evidence from the precedent versions, ensuring their relevance and accuracy over time. We found eight tools that followed this approach.[53,128,129,134,135,138,143,149]
4. *Language translation of existing tools*: Tools mainly utilized the translating approach when prescribing practices that were consistent across linguistic contexts, increasing accessibility and applicability in diverse regions. However, they employed adaptation approaches when substantial differences existed. We identified two tools developed by direct translation.[86,120]
5. *Expert-led tool development approaches*: We identified three expert-led tool development approaches. The first approach, Development of Lists and/or Algorithms Based on Expertise, involved creating tools by leveraging the knowledge and experience of certified healthcare experts. This approach aims to develop comprehensive lists and algorithms tailored to ensure medication appropriateness. The second approach was the expert-led consensus approach, where authors with different expertise collaboratively developed the initial lists and further refined them through a consensus process.[125] Additionally, the Expert-led Literature Review Approach centres on experts leading literature reviews to combine evidence and expert knowledge (ie, an initial draft list is

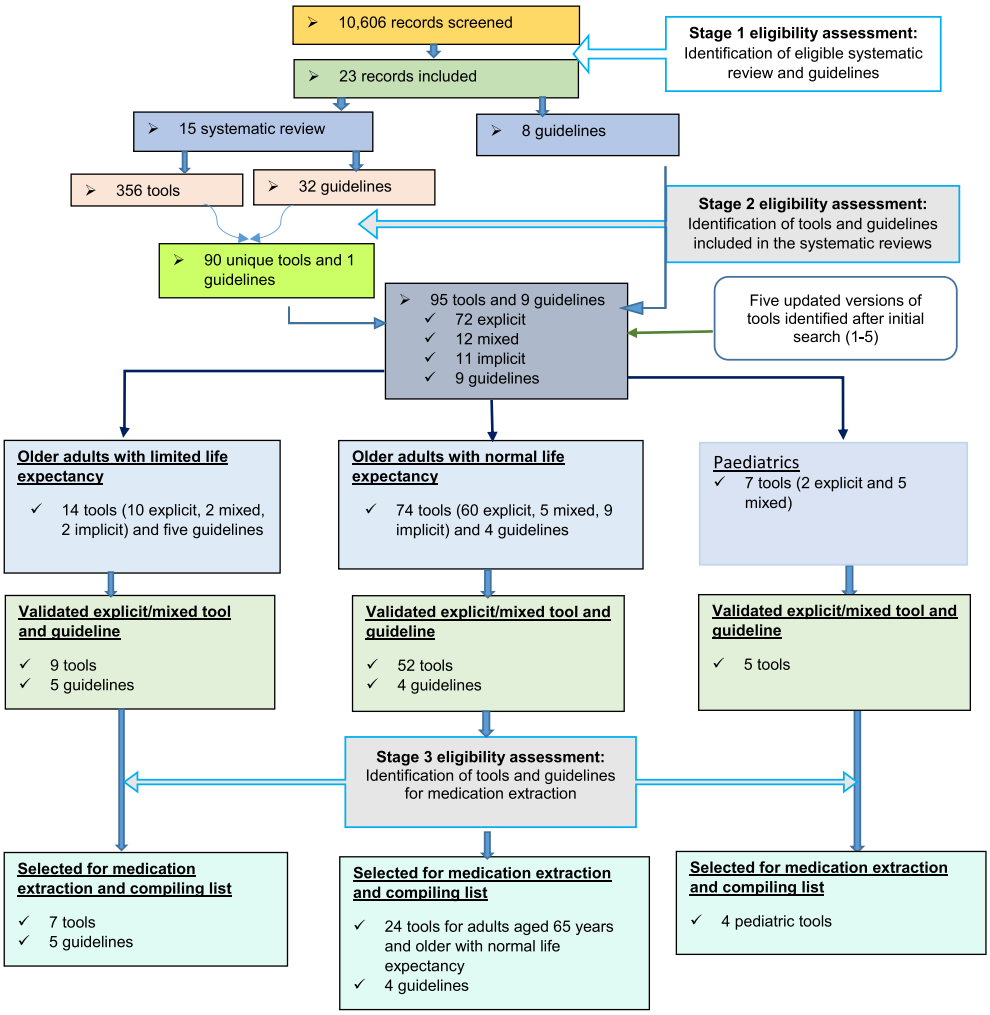

FIGURE 2 Flow diagram illustrating the progression of eligibility assessment and the application of eligibility criteria for selecting tools and guidelines, along with the key results at each stage of eligibility.

created by the authors based on their clinical experience followed by evidence generated from the literature review). This collaborative process leads to the development of robust tools that draw from both research findings and expert insights. In total, this approach was evident in five tools for patients with limited life expectancy and paediatrics, where guidelines and tools were developed through expert-led literature reviews.[62,91,105,107,125]

6. *Concept-to-list approach*: This approach involved creating tools based on a conceptual model to guide medication appropriateness decisions, ensuring a structured and conceptually sound tool development process. We found one example in tools for patients with limited life expectancy, where a disease-specific explicit tool (advanced dementia) was developed using this approach.[101] The conceptual model considered patient-related factors, such as remaining life expectancy and goals of care, as well as medication-related factors such as time until benefit and treatment target.

Tool development for paediatric and older persons with limited life expectancy relies heavily on expert-led methods, integrating clinical insights to address unique needs and complement evidence-driven strategies.

3.4 | Tools and guidelines validation approach

The explicit/mixed tools and guidelines included in our review underwent validation using various techniques. All nine of the included guidelines (100%) and a substantial majority of explicit/mixed tools ($n = 66/84$, 78.57%) underwent validation. In total, 75 tools and guidelines were validated. The detailed validation processes for each specific guideline and tool are presented in Tables 2 and 3, respectively.

3.4.1 | Consensus-based validation methods

This category encompasses validation techniques that involve reaching a consensus among experts or a guideline development team. It includes the following approaches:

1. *(Modified) Delphi technique* ($n = 58/75$, 77.3%): This technique involved iterative rounds of expert input and feedback to reach a consensus on medication appropriateness criteria. Researchers used two to four rounds for more comprehensive input and convergence of opinions.

TABLE 3 Summary of characteristics of tools to appraise the appropriateness of medications to use for different target populations.

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
Beers 1991[12,14,15,18,35]	United States	Explicit	65+ years	Nursing home	Literature (published 1979-1990 in English)	Two-round written survey based on the Delphi method with 13 nationally or internationally recognized experts from the United States and Canada (expertise in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology, general clinical geriatrics, long-term care)	30 criteria (19 criteria describing medications or medication classes that generally should be avoided, 11 criteria describing doses, frequencies or durations that should not be exceeded)
Stuck criteria 1994[14,18]	United States and Canada	Explicit	Older	Community-residing older persons	Beers 1991	Modified Delphi method (two-round) by 13 experts (geriatricians and pharmacists)	27 criteria statements
The geriatric medication algorithm 1994[12]	United States	Mixed	65+ years	Primary-care setting	Certified geriatric internists discussed the medications and develop the algorithms	Algorithm was tested in the resident outpatient clinic of a community teaching hospital	Designed to educate physicians in reducing inappropriate prescribing and divided in to four steps (The tool provide 10 medications as a high-risk drugs, less toxic alternatives for these medications and suggested drug requiring dosage reduction)
Oborne prescribing indicators 1997[12]	UK	Mixed	65+ years	Hospital setting	Based on the drug charts of 1686 patients (literature review)	Ten algorithms assessed directly from drug chart data and four requiring collection of clinical data	A list of 14 prescribing indicators that were presented in the form of algorithms guiding the user through the process of detecting inappropriate prescribing

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
Beers 1997[12,14,15,18,35]	United States	Explicit	65+ years	General ambulatory elderly population	Beers 1991 and literature (published 1990-1995 in English)	Delphi methods with two-round survey (first round, written mail survey; second round, face-to-face full-day meeting) involving six nationally recognized experts in general geriatrics, clinical pharmacology, pharmacoepidemiology, clinical pharmacy and psycho pharmacology	43 criteria statements classified as having high severity or not (28 criteria describing potentially inappropriate medications, 15 diseases or conditions and medications to be avoided in these conditions)
McLeod 1997[12,14,15,17–19,35,36]	Canada	Explicit	Older	Not reported	Beers 1991 criteria, literature (expert review of drug interactions and *Handbook of Adverse Drug Interactions*, standard textbooks on therapy provided to elderly people)	Two-round mail survey based on the Delphi method with 32 experts (seven clinical pharmacologists, nine geriatricians, eight family practitioners, eight pharmacists)	38 inappropriate high-risk practices in prescribing grouped into four categories with recommendations of alternative therapy (18 criteria generally contraindicated for elderly, 16 practices involving a drug-disease interaction, four practices involving a drug-drug interaction)
Zhan criteria 2001[12,14,17–19,35,36]	United States	Explicit	65+ years	General ambulatory elderly population	33 drugs as a subset from Beers 1997 criteria (PIM irrespective of dose, frequency of administration or duration of the therapy)	Two-round modified survey involving seven experts (five geriatricians, one	
Fick-Beers 2003[12,14,15,18,19,35]	United States	Explicit	65+ years	Ambulatory and nursing facility population	Beers 1997 criteria and literature (published	Three-round survey (first round, mail survey; second round, face-	68 criteria statements classified as having high or low severity

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
					1994-2000 in English)	to-face meeting; third round, mail survey) based on the modified Delphi method. Twelve nationally or internationally recognized experts from the United States (expertise in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology and clinical geriatric medicine) were involved	(48 criteria describing potentially inappropriate medications, 20 diseases or conditions and medications to be avoided in these conditions)
Malon list of drug-drug interactions 2004[12,19]	United States	Explicit	Not specified	Community and ambulatory pharmacy settings	Systematic review of drug interaction compendia and published literature	Three-round modified Delphi methods involving five experts (physician, clinical pharmacist and expert in drug-drug interactions)	25 clinically important drug interactions that are likely to occur in the community and ambulatory pharmacy settings were identified
Rancourt criteria 2004[12,14,17–19,36]	Canada	Explicit	Older	Long-term care facilities	Beers criteria 1991 and 1997, McLeod criteria and additional literature (four sources), excluding unavailable medications	Two rounds of the modified Delphi method by four experts	111 criteria classified into four categories (PIM, potentially inappropriate duration, potentially inappropriate dosage and potentially inappropriate drug-drug interaction)
Lindblad 2006[12,14,15,17–19]	United States	Explicit	65+ years	Outpatient	Literature published between 1966 and July 2004 (English-language articles) (eg, Beers 1997, Fick-Beers, McLeod 1997)	Two-round mail/written survey based on the modified Delphi method with nine experts (two physicians [geriatricians] and seven clinical pharmacists)	28 individual drug-disease interactions involving 14 diseases or conditions
Laroche 2007[12,14–18,35,36]	France	Explicit	75+ years	Not reported	Beers lists (1991, 1997, 2003),	Two-round mail survey based on the Delphi	34 inappropriate practices in

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
					McLeod 1997, criteria adapted to French practice and the guidelines of the French Medicine Agency on medication prescribing in the elderly	method with 15 experts (five geriatricians, five pharmacologists, two pharmacists, two general practitioners, one	prescribing with recommendations of alternative therapies (29 medications or medication classes that should be avoided, five drug-disease interactions)
Winit-Watjan 2008[12,14–19,36]	Thailand	Explicit	Older	Not reported	A literature review (databases in Thailand and worldwide) from 1990 to 2006	Delphi technique with a three-round survey of 17 experts for the first two rounds and 16 for the third round. The experts included geriatricians, geriatric medicine lecturers and physicians working in the geriatrics area	77 practice statement (33 medications or medication classes with potential adverse reactions, 32 drug-disease interactions, 12 drug-drug interactions)
STOPP/START version 1 2008[12]	Ireland	Explicit	65+ years	Community-dwelling older adults	Evidence-based literature (not defined exactly in the article), clinical experience of the investigators	Two-round mail survey based on the Delphi method with 18 experts (nine teaching hospital consultants in geriatric medicine, three clinical pharmacologists, one old-age psychiatric, two senior academic primary care physicians, three senior hospital pharmacists with interest in geriatric pharmacotherapy)	STOPP: 65 criteria focusing on prevalent problems associated with commonly prescribed medicines in older adults arranged according to physiological systems (42 criteria concerning avoidance of medications in certain disease states or conditions, four criteria concerning specific drug combinations to be avoided, 12 criteria concerning duration of drug therapies, two criteria concerning

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
							doses, three criteria concerning avoidance of prescribing without indication, two criteria concerning need for additional therapy) START: 22 evidence-based explicit prescribing indicators for common diseases in older adults
APIT 2008[12,14–16,19,35]	Australia	Mixed	65+ years	Not reported	Australian literature based on the most frequent Australian Pharmaceuticals Benefits Scheme medications prescribed to Australians in 2006, most common medical conditions for which Australians aged 65 years and older consult medical practitioners	Not validated	45 explicit and three implicit prescribing indicators (18 concerning avoidance of medications in certain disease states or conditions, 19 concerning recommended treatment in certain disease states or conditions, four concerning medication monitoring,three concerning specific drug interactions, one asking about the presence of any drug interactions, one asking about any changes in medication in the previous 90 days, one concerning smoking status, one concerning vaccination status)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
Portugal Beers criteria 2008[19]	Portugal	Explicit	65+ years	Not specified	Fick-Beers 2003	Not validated but developed based on validated Fick-Beers 2003	Included 49 drug/drug classes and PIM lists for 10 disease conditions
Prescribing optimisation method for improving prescribing in the elderly 2009[12,15,36]	Netherlands	Mixed	Older	Not reported	Based on evidence from the literature, Dutch guidelines, such as the General Practitioner Guidelines and the National Interdisciplinary Guidelines	Not validated Tested in case histories of 10 geriatric patients admitted to the geriatric outpatient clinic	Prescribing optimisation method for improving prescribing in the elderly helps physicians to optimize polypharmacy prescribing in the elderly population. This method is based on six open questions, whereby each question is presented with an overview of the most frequent and clinically relevant problems, together with explicit suggestions to improve prescribing
NORGEP 2009[12,14–19,35]	Norway	Explicit	70+ years	General practice setting (home dwelling elderly)	Beers criteria (1991, 1997, 2003), Swedish recommendations, recent evidence from literature (published 1996-2008), and clinical experience of the investigators	Three-round mail survey based on the Delphi method with 47 experts (14 clinical pharmacologists, 17 geriatricians, 16 GPs)	36 criteria for pharmacologically inappropriate prescribing in general practice (21 criteria concerning single drugs and dosages, 15 criteria concerning drug combinations to be avoided)
FORTA 2009[12]	Germany	Explicit	65+ years	Not reported	Reclassification of Beers criteria (positively and negatively)	Not validated	An expansion of Beers criteria by classifying medications in to four groups (A-D). This version of

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
							FORTA does not provide an overview of recommended drugs
PRISCUS 2010[12,14–19,36]	Germany	Explicit	65+ years	Not reported	Beers criteria 1997, Beers-Fick criteria 2003, McLeod criteria 1997, French/Laroche criteria 2007 and literature review (not specified)	Delphi method (two-round), 25 experts in the first round and 26 experts in the second round having different expertise (geriatric medicine, clinical pharmacology, general practice, internal medicine, pain therapy, neurology, psychiatry and pharmacy) participated	83 PIMs
Kim 2010[14–19]	Korea	Explicit	65+ years	Outpatient setting	Beers criteria, Canadian criteria and Zhan's classification (adapt to Korean reimbursed drug list) and classified lists based on Fialova et al criteria[53]	Delphi evaluation with a two-round survey included 14 geriatric specialists, including seven family medicine specialists, three psychiatrists, one neurologist and three clinical pharmacists	57 potentially inappropriate drugs for the elderly, independent of diagnosis, 93 potentially inappropriate drugs in 29 diagnoses (48 individual medications or classes of medication to avoid in older adults and their potential concerns and 20 disease/conditions and medication to be avoided in older adults with these conditions)
New Mexico criteria 2012[12,14,18]	United States	Explicit	65+ years	Not reported	Fick-Beers 2003	Delphi method (two-round) involving 12 experts (clinical pharmacists, geriatricians, nurses,	72 drugs to be used with caution in the elderly

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
						managed care specialists and consumers)	
Matanovic 2012[14–16,19,36]	Croatia	Explicit	65+ years	Ambulatory and clinical settings as well as nursing homes	Explicit screening tools for PIMs already published but adjusted (McLeod 1997, Fick-Beers 2003, Lindblad 2006, Laroche 2007, Malone 2004, Hanlon 2005)	Not validated	In total 110 drugs (33 criteria with unfavourable risk:benefit ratio, six questionable efficacy and 71 individual drug-disease interactions involving 28 diseases or conditions)
Chang 2012[14–16,18,36]	Taiwan	Explicit	65+ years	Not reported	Beers-Fick 2003, McLeod criteria 1997, Rancourt 2004, French criteria 2007, STOPP/START version 1, NORGEP 2009 and Thailand criteria 2008 (availability checked)	Delphi method (two-round) involving 21 experts from various specialties (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 six drug or drug classes that patients with these conditions should avoid)
Mann 2012[12,14–19,36]	Austria	Explicit	65+ years	Not reported	Beers criteria 1997, Beers-Fick criteria 2003, McLeod criteria 1997, Laroche criteria 2007, STOPP/START version1 and PRISCUS 2010	Modified two-round Delphi method that involves eight experts (GP, a specialist in neurology, three specialists in internal medicine, a psychiatrist and two clinical pharmacists working in hospital)	73 drugs to be avoided in older patients because of an unfavourable benefit/risk profile and/or unproven effectiveness
Beers 2012[12,14,15,18]	United States	Explicit	65+ years	All ambulatory and institutional care settings	Update of Fick-Beers 2003 criteria by literature review from 1 December 2001 (the end of the previous panel's	Modified Delphi method (a conference call and a 2-day in-person meeting) with 11-member interdisciplinary expert	53 medications or medication classes encompass the final updated criteria (34 medications or medication classes

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
					search) to 30 March 2011	panel (expertise in geriatric medicine, nursing, pharmacy practice, research and quality measures) and representatives from different organizations	to avoid in the elderly, 14 diseases and conditions and medications to be avoided in these conditions, five medications to be used with caution in older adults)
APIT 2012[14,17,18,36]	Australia	Explicit	65+ years	All settings	Basager 2008 and literature in the context of Australia by identifying common problems by obtaining healthcare information using the Bettering The Evaluation and Care of Health (BEACH) programme	RAND/UCLA appropriateness method, a two-round modified Delphi method involving 15 experts in the first round and 12 in the second (geriatricians/ pharmacologists, clinical pharmacists, disease management advisors to organizations that produce Australian evidence-based therapeutic publications)	41 criteria
Clyne criteria 2013[14,18,19]	Ireland	Explicit	65+ years	Primary care settings	Mcleod 1997, IPET, Beers criteria 2012, Prescription Peer Academic Detailing (Rx-PAD) study, ACOVE-3, and STOPP version 1	Two-round Delphi method and focus group involving five experts (two GPs, two pharmacists, one physician)	34 criteria
PIMHF 2014[15,17,19]	Ireland	Explicit	Older	Ambulatory heart failure population	Literature search (January 1960 to 31 December 2010, English language publication)	Two-round modified Delphi method (22 experts with multidisciplinary team involved), electronic approach (no face-to-face meetings)	11 disease-specific lists (heart failure)
RASP list 2014[14,17,36]	Belgium	Explicit	Older	All healthcare settings	STOPP version 1	Content Validity Index method, including 19 experts, response in	76 criteria

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
						two rounds (five pharmacists, four geriatricians, five hospital pharmacists, five geriatricians)	
FORTA 2014[14,16,18,19,36]	Germany and Austria	Explicit	Older	Not reported	FORTA publication[54]	Two-round Delphi procedure was conducted involving 20 experts, 17 geriatric internists and three geriatricpsychiatrists. The experts were participated from Germany (13-experts) and Austria (7-experts)	Classify 190 medications/ medication classes into four categories: A, Absolutely, indispensable drug, clear-cut benefit in terms of efficacy/ safety ratio proven in elderly patients for a given indication); B, Beneficial, drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns); C, Careful, drugs with questionable efficacy/safety profiles in the elderly, to be avoided or omitted in the presence of too many drugs, lack of benefits or emerging side effects, review/find alternatives; D, Do not, avoid in the elderly, omit first, review/find alternatives
High-risk medications 2015[19]	United States	Explicit	Older	Not reported	Comprehensive literature review from 2000 to 2015	Not formal validation procedure, but the lists developed by consulting	Provide the list of drug therapy alternatives with supporting

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
					(three experts developed the list of alternatives based on the literature)	the explicit expert panel consensus criteria and received feedback from the National Committee for Quality Assurance, the Pharmacy Quality Alliance, the 2015 American Geriatrics Society Beers Criteria panel and the Executive Committee of the American Geriatrics Society	references. Alternatives for high-risk medications organized into 15 therapeutic classes according to the measure specifications for high-risk medications published in 2015. 10 therapeutic drug classes that are included in the Potentially Harmful Drug-Disease Interactions in the Elderly measure (a prior history of falls, dementia, and chronic kidney disease). nonpharmacological alternatives was also provided.
Beers 2015[14–16,18,36]	United States	Explicit	65+ years	All ambulatory, acute and institutionalized settings with the exception of hospice and palliative care	Beers 2012, literature review (from 1 August 2011 [the end of the previous panel's search] to 1 July 2014), English language	Modified Delphi method (two rounds) with a 13-member interdisciplinary expert panel, 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

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
							inappropriate medications based on kidney function)
Spanish adaptations of Beers criteria 2015[19]	Spain	Explicit	Elderly	Not reported	Beers 2012, STOPP/START 2008, PRISCUS, NORGEP 2009	Not validated but developed based on explicit screening tools for PIMs already published	47 (34.3%) active substances were not commercially available in Spain and 40 new ones could be included in the Beers 2012 list. For disease-dependent criteria the figures were 33 (21.3%) and 48, respectively
EU (7)-PIM list 2015[14–16,18,19,36]	Seven EU countries[a]	Explicit	65+ years	Not reported	PRISCUS 2010, French criteria 2007, Beers criteria 1997, Beers-Fick criteria 2003, McLeod criteria, Beers criteria 2012 and Micromedex	Delphi method (two rounds), In the first delphi 26 experts participated out of 29 invited experts whereas in the second round 24 experts were participated out of 28 invited experts. The expert panel included clinical pharmacologist, pharmacist, nursing scientist, geriatrician. Finally based on the information obtained from the, 2 rounds, a reduced number of experts were participated in brief survey (12 participated/12 invited) to finalised the list.	282 drugs/drug classes and preparations were classified as medication inappropriate PIMs for older people; some PIMs are restricted to a certain dose or duration of use, non-PIMs (three drugs), questionable PIMs (29 drugs)
STOPP/START version 2 2015[14–19,41]	Ireland (13 EU countries)[b]	Explicit	65+ years	All care settings	STOPP/START 2008 and literature review after 2008	Delphi method (two rounds), 19 experts (expertise in geriatric medicine and pharmacotherapy in older people)	Final list of 114 criteria (80 STOPP criteria and 34 START criteria)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
STOPP-START Spanish 2015[19]	Spain	Explicit	65+ years	All care settings	STOPP/START 2015	Language translation	Review of Spanish study on prevalence of inappropriate prescription based on Spanish STOPP-START 2009 criteria and list of Spanish translations of STOPP-START 2015 criteria. Final list included 114 criteria (80 STOPP and 34 START)
Kim criteria 2015[14,16–19]	Korea	Explicit	65+ years	Long-term care services	Beers 2012, STOPP version 1 and PRISCUS (intersectional list)	Delphi method (two rounds), 20 experts (14 physicians and six pharmacists)	26 ingredients from seven drug classes were selected as PIM candidates
GheOP^{3}S 2016[14,18,36]	Europe (Belgium)	Explicit	Older	Community pharmacy setting	Literature review of previously published tools (between January 1990 and December 2012)	RAND/UCLA (two rounds), 11 experts (clinical pharmacists, geriatricians, GPs, academics, community pharmacist, physician)	83 items for identifying PIPs (31 potentially inappropriate drugs, independent of diagnosis, 11 potentially inappropriate drugs, dependent on diagnosis, six PPOs, 29 drug-drug interactions of specific relevance, six general care-related items to be addressed in the community pharmacy)
FORTA version 3 2018[17]	Germany, Austria, Switzerland	Explicit	65+ years	Not reported	FORTA 2014	Two-round Delphi method involving 22 experts (geriatric internists, geriatric psychiatrists)	296 substances/ substance groups aligned to 30 indication groups

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
EURO-FORTA 2018[17,19]	EU (7)[c]	Explicit	65+ years	Not reported	Explicit screening tools for PIMs already published (FORTA)	Delphi consensus validations (two rounds) involving geriatrician neurologist and clinical pharmacist (47-experts participated in the delp)	Seven new country/region-specific FORTA lists, list containing 264 items in 26 main indication groups
Korean PIM 2018[17,19]	Korea	Explicit	Older	All care settings outside palliative care setting	Beers 2015, STOPP 2, PRISCUS, PIM list for the Korean Elderly 2010, PIM list for the Korean Health Insurance Review and Assessment Service and the PIM list for the Seoul National University Bundang Hospital	Four-round modified Delphi method (expert panel consisted of 14 geriatric specialists, including 10 geriatricians [seven family medicine doctors and three internal medicine doctors], three geriatric psychiatrists and one clinical pharmacist)	110 drugs and classes (62 drugs were classified as PIMs for older adults irrespective of comorbidities and 48 drugs or drug categories were classified as PIMs for 18 specific conditions that older adults encounter frequently)
The updated PIM-Taiwan criteria 2019[17,19]	Taiwan	Explicit	65+ years	Not reported	Beers 2015, Japan criteria, FORTA and STOPP version 2	Two rounds of modified Delphi methods (24 geriatricians, neurologists, psychiatrists, cardiologists, pulmonologists, gastroenterologists, urologists, clinical pharmacists)	131 individual drugs and nine drugs with combinations that should generally be avoided, nine chronic diseases with their corresponding PIMs that have drug-disease interactions
ES-PIA Project (Gonzalez criteria) 2019[17,19]	Spain	Explicit	65+ years	Not reported	Previously published criteria, including screening tools, product information summaries and pharmaceutical adverse events database	Two-round Delphi method involving 25 experts from different backgrounds (clinical pharmacology, geriatrics, rational use of drugs and pharmacy, primary care, and pharmacoepidemiology and pharmacovigilance)	138 statements
Beers 2019[14,17,19,41]	United States	Explicit	65+ years	All healthcare settings except hospice and	Beers 2015 and literature review from 1 January	Modified Delphi method, interdisciplinary panel of 13 experts in	114 medications/class to be avoided, 37 medication/

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
				palliative care settings	2015 to 30 September 2017	geriatric care and pharmacotherapy	medication classes interacted with 10 syndromes, 17 drug-drug interactions, 23 medications/ medication classes should be avoided or have their dosage reduced with varying levels of kidneyfunction and 15 medication/ medication classes. Drugs to be used with caution
Angular criteria 2019[19]	Portugal	Explicit	65+ years	Not reported	24 explicit tools in the literature	Not validated	115 PIMs with risk of cardiovascular adverse events to be avoided in elderly patients and seven drug-disease interactions
Modified STOPP/ START Sri Lanka 2019[19]	Sri Lanka	Explicit	Older	Not reported (in the context of resource-limited healthcare settings)	STOPP START version 2	Two-round Delphi consensus methodology involving six experts, including geriatricians, clinical pharmacologists, physicians and a pharmacist, to review and assess each criterion (including the ones flagged by the researchers)	List of 105 criteria, including 70 STOPP and 35 START criteria, indicating an 8% reduction in criteria compared to the original version. Modifications included complete removal ($n = 11$), re-wording ($n = 25$), splitting ($n = 1$) of original criteria and adding a new criterion ($n = 1$)
Motter Brazilian consensus PIM 2019[19]	Brazil	Explicit	65+ years (pain and inflammation)	Not reported	Beers 2015, STOPP version 2, EU (7)-PIM list	Online two-round modified Delphi technique (13 experts who agreed to participate in the study,	33 concerns about drugs that should be avoided in older patients regardless of diagnosis, 22

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
						10 were geriatricians and three were pharmacists, of these nine was participated in the first round and seven in the second round). All participants were geriatricians with more than 10 years of experience in geriatric medicine	concerns about drugs that should be avoided in older patients with specific conditions or diseases, 11 concerns with special considerations of use, and 28 concerns of therapeutic alternatives
TIME 2020[17,19]/ TIME 2021 validation study[19]	Turkey	Explicit	Older	All care settings	STOPP/START version 2 and CRIME criteria[55]	Three-round Delphi method with 11 experts (nine academic geriatricians, one clinical pharmacologist, one community pharmacist academic). Seven countries in Europe (Belgium, Czech Republic, Germany, Italy, Spain, UK, the Netherlands) and one from Israel	Internationally validated version of the TIME criteria, includes 134 criteria (101 TIME-to-STOPP and 33 TIME-to-START criteria)
US-FORTA 2020[17,19]	United States	Explicit	65+ years	Not reported	The EUROFORTA list, validated FORTA (VALFORTA), oral anticoagulants (OAC-FORTA specific lists)	A two-step Delphi-type approach with eight experts (geriatricians, pharmacists)	Contains 273 items aligned to 27 main indication groups
JAPAN-FORTA 2020[17,19]	Japan	Explicit	65+ years	Not reported	The EUROFORTA list, validated the FORTA (VALFORTA), oral nticoagulant (OAC-FORTA specific lists)	Two-step Delphi consensus validation by 13 experts (geriatricians, pharmacists, cardiologists)	Contains 210 items aligned to 24 main indication groups
STOPP Indonesia 2020[19]	Indonesia	Explicit	Older	Hospital	STOPP-START version 2 (developed with the	Psychometric test for validation and expert team of eight experts	The expert team was agreed on 81 criteria (100%) of

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TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
					cross-cultural adaptation guidelines from the American Association of Bone Surgeons Committee)	consisting of two geriatricians, one pharmacologist, one endocrinologist, one cardiologist, one neurologist, one clinical pharmacist and one linguist who was also a translator member	adaptation of STOPP version 2 criteria. There were five criteria that were not valid statistically. They could not be removed from the instrument because they can influence the content and construct of the instrument
STOPPFall 2020[17]	EU	Explicit	Older	General geriatric setting	Three recently published systematic reviews and meta-analyses and eight national falls prevention guidelines in Europe	A three-round modified Delphi technique involving 24 experts (20 geriatricians, three pharmacists, one general practitioner)	14 medication classes to be included in STOPPFall
EU (7)-PIM list French 2020[19]	France	Mixed	Older	Not specified	EU (7)-PIM adaptation and implicit tool: the recommendations of the French National Health Authority (HAS) and more specifically the "alerte et maitrise de la iatrogénie" (AMI tools)	Not validated	From 289 PIMs identified in the EU (7)-PIM list, 183 drugs were included the list. Three PIMs were added to the list of "questionable" PIMs in accordance with the new French recommendations
Hong Kong criteria 2021[17,19]	Hong Kong	Explicit	65+ years	All healthcare settings	Explicit tools assessing PIM use on the PubMed database from January 1991 to April 2019 internationally (nine sets of explicit criteria were included as reference criteria: the McLeod criteria,	Two rounds of the modified Delphi process (in total 8-experts were participated: 4 geriatric physcians, 3 pharmacists, and 1 general practicioner)	PIM list included a total of 164 statements applicable to adults aged 65 years or above, among which 77 were under PIMs independent of diagnoses and 87 were under PIMs considering specific

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
					the Rancourt criteria, the Lindblad criteria, the Laroche criteria, the Winit-Watjana criteria, the Norwegian General Practice, the PRISCUS criteria, STOPP version 2 and Beers 2012)		medical conditions. Eight PIM candidates remained questionable and thus were excluded from the PIM list
PIMHF 2021[17]	Thailand	Explicit	Older	All care settings for patients with heart failure	Heart failure guidelines, heart failure-related explicit criteria and literature review (Beers criteria 2015, STOPP criteria 2015, St Vincent's list of PIMHF 2014 and AHA scientific statement 2016)	Three-round modified Delphi technique involving 17 experts (10 cardiologists, three hospital pharmacists, four academic pharmacists)	47 medication items reached the consensus and agreed as PIMHF
GheOP3S version 2 2021[17,19]	Belgium	Explicit	65+ years	Primary care setting	GheOP3S version 1 and recent scientific evidence (Beer 2019, STOPP version II and NORGEP-NH)	Two-round modified Delphi process according to the RAND/UCLA appropriateness method with 26 experts (new panel appointed for each round. Round 1: six geriatricians, two academics, two clinical pharmacists, two GPs, one emergency physician, one community pharmacist, one nurse. Round 2: three geriatricians, two clinical pharmacists, two GPs, one emergency physician, one community pharmacist, one hospital pharmacist, one nurse)	64 criteria and can support pharmacists to consolidate their role as medication experts by reducing polypharmacy inappropriateness and/or by optimizing patients' medication use in primary care.

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
EU (7)-PIM criteria, Portugal 2021[19]	Portugal	Explicit	Older	Not reported	EU (7)-PIM and identification of possible PIMs available in the Portuguese market and not included in the EU (7)-PIM list	Not validated	184 potentially inappropriate medicines (from these, 178 were active substances, five were classes of drugs and one corresponded to the sliding scale therapeutic scheme used in insulin therapy). Of 1089 polymedicated older patients, 83.7% took at least one drug included in the final PIM list or belonging to one of the groups included in the list
FORTA List 2021 2022[56]	Germany, Austria and Switzerland	Explicit	65+ years	Not specified	Developed based on the existing FORTA version 3, which updated with new evidence and experiences	Delphi technique conducted online in two rounds with 20 experts	295 items aligned to 30 indications, with four new substances/ indications suggested by experts
EURO-FORTA 2023[57]	EU (7)-PIM[c]	Explicit	65+ years	Not specified	Developed based on the existing Euro-FORTA lists, updated with new evidence and experiences	Delphi technique conducted online in two rounds with 32 experts and a return rate of 96.9%	267 items aligned to 27 indications. Three items were added to the EURO-FORTA list and no drugs were deleted. Eight FORTA items were relabelled from EURO-FORTA version 1
Beer 2023[58]	United States	Explicit	65+ years	All ambulatory, acute and institutionalized settings of care,	Beer 2019 and literature search via PubMed from 1	Two rounds of modified Delphi method with an expert panel of 12	107 medications/ classes to be avoided, 39

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
				except hospice and end-of-life care settings	June 2017 to 31 May 2022	interprofessional members drawn from medicine, nursing and pharmacy	medication/ medication classes interacted with nine disease/syndromes, 18 drug-drug interactions, 18 medication/ medication classes to be used with caution, 24 medications/ medication classes should be avoided or have their dosage reduced with varying levels of kidney function
STOPP-version 3 2023[59]	Ireland (representing eight European countries)	Explicit	Older	Not reported	Published literature from April 2014 to March 2022	Four rounds of an online Delphi validation panel of 11 academic physicians with recognized expertise in geriatric pharmacotherapy from eight European countries (northern, southern, eastern and western Europe, ie, a broad range of European clinical practice and perspective)	The number of STOPP criteria increased from 80 to 133 and the number of START criteria increased from 34 to 57 in version 3 compared to version 2. In total, there are now 190 STOPP/ START criteria, representing a 66.7% increase compared to STOPP/START version 2 published in 2015
PRISCUS 2023[60]	Germany and Austria	Explicit	65+ years	Not reported	PRISCUS list 2010 and systematic review for new update and/or revision	59 people took part in a three-round Delphi process, with experts from clinical practice and research	187 substances were classed as PIMs, 133 of the substances now listed were not in the original PRISCUS lists
Tools developed to use for frail elderly with limited life expectancy/end-of-life							
	United States	Explicit					

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
Holmes, 2008[14,19,36,40]			Older persons with dementia	Long-term care facilities	Literature review of medication use for palliative care for elderly with dementia ("Reconsidering Medication Appropriateness for Patients Late in Life")	Three-round modified Delphi process with 12 geriatricians. A medication or medication class was defined according to agreement on categorization by at least seven of the 12 respondents	79 medications and medication classes (12 always appropriate, 30 sometimes appropriate, 14 rarely appropriate, 10 never appropriate and 12 no consensus achieved)
Patient-centred prescription model in elderly at the end of life 2015[40]	Spain	Mixed (framework combines both clinical judgement and scientific evidence)	85+ years and/cognitive impairment, individuals with LLE	Acute care elderly unit	Multidisciplinary team made up of geriatricians and a clinical pharmacist developed the model and appraisal of medication	Not provided (applied to 309 patients admitted in acute care and high-prevalence of inappropriate prescribing was identified).	Model for assessing pharmacotherapy, including considerations for discontinuing medications. Patient-centred prescription mode involving a three-step process to develop a therapeutic plan (patient-centred evaluation, diagnosis-centred evaluation and medication-centred assessment)
OncPal deprescribing guideline 2015[19,41]	Australia	Explicit	Palliative cancer patients with an estimated <6-month prognosis	Palliative cancer inpatients	Literature for the de-escalation of medications by systematically reviewing each medication class according to the European Pharmaceutical Market Research Association anatomical classification list	The guideline was validated by applying it to 61 patients (617 medicines = 10 per patient) and comparing the agreement between the pharmacist applying the guideline and the expert panel to decide whether the medications were PIMs or not. The agreement level was 94%. A single-	24 medication/ medication classes

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
						phase consensus model was used, sending the draft guideline to three palliative care consultants, three oncology consultants and three senior pharmacists for their feedback	
NORGEP-NH 2015[14,15,17–19,36]	Norway	Explicit	70+ years	Nursing home residents (frail)	Norwegian general practice (NORGEP 2009) criteria, literature and clinical experience	Web-based three-round Delphi consensus process (62 in the first round, 52 in the second round and 49 in the third round), with experts (15 geriatrics specialists, five clinical pharmacology specialists, five pharmacists, nursing home physicians or members of the General Practitioners' Reference Groups for Nursing Home Medicine (24)	34 explicit criteria for PIMs (11 single substances criteria/ regular use should be avoided, 15 drug-drug combination criteria, eight with regular consideration of deprescribing)
Algorithm of medication review in frail older people 2016[19]	Australia	Mixed (algorithm and list of criteria)	Older (frail older people)	Residential aged-care facilities	Literature review (Beers criteria 2012, McLeod criteria, Laroche list, PRISCUS list and the Norwegian General Practice criteria)	Not validated	Algorithm comprised several steps leading to individualized prescribing recommendations: (i) identify a high-risk medication; (ii) ascertain the current indications for the medication and assess their validity; (iii) assess if the drug is providing ongoing symptomatic benefit; and (iv) consider withdrawing, altering or

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TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
							continuing medications. Includes PIM lists and withdrawal regimens for commonly used medications in older people and alternative management strategies for commonly used PIMs
Futility criteria by Oliveira et al, 2016[41]	Portugal	Explicit	Advanced cancer patients with a life expectancy <6 months	Oncology setting	Fede criteria of unnecessary medication use by advanced cancer patients, 2011[61]	Not validated	Criteria for futility of seven medication categories, criteria modified from Fede et al.[61] Medication categories included conditions for futility. Medication categories covered gastric protectors, antihypertensive drugs, antidiabetic drugs, statins, anticoagulants, bisphosphonates and antidementia drugs
MATCH-D 2016[17]	Australia	Explicit	65+ years (dementia and comorbidity)	Not reported	Expert opinion	Three-round online Delphi method involving multidisciplinary expert panel consisting of 57 experts with qualifications and experience in relevant fields (33 pharmacists, four GPs, one clinical pharmacologist,nine geriatricians, five physicians, one general medicine physician, one	The participants reached consensus on 111 of 128 statements. Of these statements, 67 statements were included in the Medication Appropriateness Tool for Co-morbid Health conditions in dementia criteria

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
						research psychologist, two registered nurses, one nurse practitioner, one patient advocate)	
LESS-CHRON 2017[40]	Spain	Explicit	Older persons with multiple comorbidities, specifically frail older persons (criteria are medication-specific)	Not reported	Literature (Spanish and English, September 2013) and electronic brainstorming	Two online Delphi methods (11 experts included four specialists in hospital pharmacy, three in internal medicine, three GPs and one primary care pharmacist)	The final list included 27 criteria and each of the criteria contained drug indications for which that drug could be prescribed, a clinical situation that offers an opportunity to deprescribe, a clinical variable to be monitored and the minimum time to follow up the patient after deprescribing
STOPPFrail 2017[19,40]	Ireland	Explicit	Frailer older adults with LLE (65+ years)	All healthcare settings	Clinical experience of authors and literature review of the last 20 years	Three Delphi rounds involving 17 expert panels (six consultant geriatricians, three clinical pharmacologists, one old age psychiatrist, three palliative care physicians, two senior academic primary care physicians and two clinical pharmacists with an interest in geriatric pharmacotherapy)	27 criteria relating to medications that are potentially inappropriate in frail older patients with LLE
STOPP/START (United States) 2017[14,18,19]	United States	Explicit	65+ years very frail older adults with less than 1 year to live	Nursing home residents	STOPP/START version 2	E-Delphi panel consisted of three rounds: initial assessment, feedback and discussion, final assessment (17 participated in round 1, 15 of whom participated in round 2 and 11 in round 3). The	24 criteria (22 PIMs, two underused medications criteria)

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
						experts were five pharmacists, five nurses, four researchers and three physicians	
Morin European consensus criteria 2018[19]	10 European countries[d]	Explicit	75 years or older (estimated life expectancy of ≤3 months)	Not specified	Systematic review of the literature updating the findings from Todd et al	Two-round Delphi (40 experts in the first round and 39 in the second), the expert panel included 13 geriatricians, 12 palliative care physicians, seven GPs, seven pharmacists or clinical pharmacologists and one palliative care psychiatrist	Provide a list for continuation of previously prescribed drug classes (14 drug classes deemed as often adequate, 28 drug classes deemed questionable and 10 drug classes deemed often inadequate), initiation of new drug treatments (10 drug classes deemed often adequate, 23 drug classes deemed questionable and 23 drug classes deemed often inadequate)
STOPPFrail 2021[17]	Ireland	Explicit	Older adults with LLE	All care settings for frail patients with LLE	STOPPFrail version 1, literature and expert opinion	Two round Delphi method (panel comprised eight experts: three in geriatric medicine, two in clinical pharmacology, one in psychiatry of older age, one in general practice and one in palliative medicine)	A new method for identifying older people who are likely to be approaching end-of-life was included, along with 25 deprescribing criteria that included a general guide, system-based drugs and miscellaneous
Tools developed for use with special target groups							
The List of High-risk Perioperative Medications for Elders in China 2019[17,19]	China	Explicit	Older	Perioperative setting	Literature review published before March 2018	Two-round Delphi (36 experts: six geriatricians, six anaesthesiologists, six surgeons and 18 pharmacists)	A total of 86 medications in 13 medication classes and 120 screening items were included in the final list, along

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
							with perioperative risk profiles and risk aversion recommendations for each drug
PIM-Check 2017[14]	Canada, Belgium, France and Switzerland	Explicit	Adult	Adults in internal medicine (excluding pregnant women and inpatients with LLE or requiring palliative care)	For each medical domain and subdomains selected during the first step, an extensive literature review of evidence-based optimal and inappropriate medication prescriptions was conducted	Two-round Delphi survey (39 experts participated from 40 invited, in both the first and second rounds) that involved internist and clinical pharmacist	160 statements in 17 medical domains and 56 pathologies
Explicit/mixed tools developed for use in children							
POPI 2011[39]	France	Mixed	Less than 18years	All paediatric practice settings	Internal expert consensus and citing literature for each list	Not validated	Nine partial lists (five inappropriate prescription and four omissions of prescription)
POPI 2014[38,39]	France	Mixed	Less than 18 years	All paediatrics settings	Literature published after 2000 (including French and international guidelines)	Two-round-Delphi consensus technique (16 experts: pharmacists and eight paediatricians, 50% hospital-based and 50% or working in the community)	105 (80 PIMs and 25 PPOs
POPI 2016[39]	France	Mixed	Le18– years	All paediatrics settings	Literature published after 2000 (including French and international guidelines)	Two-round Delphi consensus technique (16 experts: pharmacists and eight paediatricians, 50% hospital-based and 50% working in the community)	101 criteria were selected (76 inappropriate prescriptions and 25 omissions)
Potentially inappropriate prescribing in children 2016[38,39]	Ireland and UK	Explicit	16– years	Primary care	Literature review, guidelines produced by different societies, networks and institutions	Two-round modified Delphi consensus method (15 experts consisting of GPs, pharmacists and	12 (5 PPOs and 7 PIMs)

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
						paediatricians from the Republic of Ireland and the UK)	
Modified POPI (UK) tool 2017 (short version),[38,39] modified POPI (UK) tool 2019 (full version)	UK	Mixed	Less than or equal to 18 years	All paediatric practice settings	POPI 2014	Not validated, a modification of POPI 2014	80 (60 PIMs and 20 PPOs)
KIDs List 2020[38]	United States	Explicit	Less than 18 years	All care settings	Literature review (English language)	Expert consensus panel (seven paediatric pharmacists) through the GRADE framework	77 PIMs (67 drugs and 10 pharmaceutical excipients)
POPI Int 2020[38]	Multi-national consensus[e]	Mixed	Less than 18 years	Primary care	Adapting POPI France (updated POPI 2016) based on the context of countries	Two-round online Delphi consensus method (20 in the first round, 11 pharmacists and nine physicians, and 14 in the second round)	73 (58 PIMs and 15 PPOs)
Implicit tools/tools with scoring systems							
MAI 1992[12,35,36]	United States	Implicit	Adults (the tool was developed and tested based on data from older persons (65^{+} years), but its use is not restricted to this age group).	Not reported	Literature (Medline and manual search) published 1982-1990, clinical experience of a clinical pharmacist and an internist geriatrician	MAI: convenience sample of 10 academic healthcare professionals judged MAI items to be definitely important or moderately important, providing an independent validation of their suitability	Ten criteria (indication, effectiveness, dosage, correct directions, drug-drug interactions, drug-disease interactions, practical directions, costs, duplication, duration) worded as questions to assess the appropriateness of each prescribed drug with instructions for use and operational definitions for each criterion
Lipton 1992[12]	United States	Implicit	65+ years	Outpatient setting	Expert	Not reported	Evaluation of each drug in the patient's

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
							regimen in seven categories of potential drug therapy problem. For each category a score of 0-9 is given
Hamdy criteria for medication profile review in extended care 1995[12]							
Robertson's flow charts 1996[12]	United States	Implicit	Not specified	Hospital settings	Not reported	Not reported	Flow chart encouraging a uniform approach to preventing, identifying and correcting drug therapy problems
Cantrill indicators of the appropriateness of long-term prescribing in general practice 1998[12]	UK	Implicit	Not specified	Long-term care (nursing homes)	Expert	Nominal group was used to identify potential indicators of appropriateness of prescribing and two-round Delphi exercise used for validation (composed of 100 GPs and 100 community pharmacists)	Nine indicators of prescribing appropriateness for assessing the entire drug regimen of patients on long-term medications in general practice
Barenholtz self-administered medication risk questionnaire in an elderly population 2003[12]	United States	Implicit	60– years	Not specified	Literature	Not reported	Ten-item questionnaire for use by elderly patients to help in identifying who is at increased risk of medication-related problems
Sedative load 2003[36]	Finland	Implicit (scoring)	Older	Home-dwelling elderly	Drugs approved for prescription in Finland in 1998-2001 having sedative effects	Expert panel and classifications applied in 1998-99 to a cross-sectional survey of home-dwelling elderly subjects ($n = 1197$, 43% men) aged 64-97 yearsin Lieto, a semirural community in southwestern Finland	List of medicines with a proper or potential sedative effect (primary sedatives, drugs with sedation as a prominent side effect or preparations with a sedating component, drugs

(Continues)

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
							with sedation as a potential adverse effect). (Anticholinergic)
Anticholinergic Risk Scale 2008[36]							
Comorbidity-polypharmacy score 2011[36]	United States	Implicit (scoring)	45+ years	Trauma setting	A total of 323 patients were examined who were using an average of 4.74 pre-injury medications	Not reported	Comorbidity-polypharmacy score was defined as the number of pre-admission medications plus comorbidities
Implicit tools developed for use in frail elderly/limited life expectancy							
Holmes reconsidering MAI 2006[40]	United States	Implicit (conceptual model)	65^{+} years individuals with LLE	Not specified	Not clear (it seems the author developed the model themselves)	Not specified (but three case scenarios used to demonstrate how this approach may aid individualized decision making regarding medication discontinuation)	Four components in a model of appropriate prescribing late in life: remaining life expectancy, time until benefit, goals of care, and treatment target
Geriatric-palliative algorithm 2007[40]	Israel	Implicit	Frail older persons (nursing home residents with incurable disease)	Nursing homes and nursing departments	Not clear (it seems the author developed the algorithms themselves)	119 disabled patients in six geriatric nursing departments; the control group included 71 patients of comparable age, gender and co-morbidities in the same wards. After 12 months, they assessed whether any change in medications affected the death rate, referrals to acute care facility and costs. Application of the geriatric-palliative methodology in the disabled elderly enables simultaneous	Algorithm aimed at identifying whether a drug can be deprescribed based on indication, safety and alternative therapies

TABLE 3 (Continued)

Tool name	Country	Nature of the criteria	Target age group	Setting	Development/base of the criteria	Validation methods (composition of experts)	Content of the criteria[f]
						discontinuation of several medications and yields a number of benefits: reduction in mortality rates and referrals to acute care facilities, lower costs and improved quality of living	

Abbreviations: ACOVE-3, Assessing Care of Vulnerable Elders; APIT, Australian Prescribing Indicators Tool; EU, European Union; FORTA, Fit fOR The Aged; GP, general practitioner; LESS-CHRON, List of Evidence-based Deprescribing for Chronic Patients; LLE, limited life expectancy; MAI, medication appropriateness index; MATCH-D, Medication Appropriateness Tool for Comorbid Health Conditions in Dementia; PIM, potentially inappropriate medications; PIMHF, potentially inappropriate medication for heart failure; PPO, potential prescribing omission; RAND/UCLA, University of California at Los Angeles; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NORGEP, the Norwegian General Practice.

[a]Estonia, Finland, France, German, the Netherlands, Spain and Sweden.

[b]The UK, France, Spain, Italy, the Netherlands, Denmark, Czech Republic, Poland, Iceland, Belgium, Switzerland, Austria and Germany.

[c]The UK/Ireland, France, Poland, Italy, Spain, the Nordic countries and the Netherlands plus the original FORTA (Germany and Austria).

[d]Belgium, France, Germany, Italy, Norway, Portugal, Spain, Sweden, Switzerland and the UK.

[e]England, Belgium, Brazil, Canada, China, Ivory Coast, Ireland, Malaysia, Portugal, Switzerland, Turkey and Vietnam.

[f]Most of the tools use one of three rating scales: five-point Likert scale [1-5], nine-point Likert scale [1-9], 1 to 4 rating scale of FORTA-based tools. The decision to include the proposed medications/medication classes in the tools was based on the analysis of the experts' responses from the Likert scale. These tools used a median or mean score with 95% confidence interval (CI). The cut-off to classify the drug as a PIM slightly varied between tools (eg, EU (7)-PIM list classifies drugs as PIMs if both the mean value of the score and the upper limit of the 95% CI are lower than 3, whereas the updated PIM-Taiwan criteria, 2019 used a mean score of 3.5 as a cut-off.

TABLE 3 (Continued)

Tool name	Aspects of PIMs covered by the lists							
	PIMs independents of diagnosis	Stopping criteria	Starting criteria	Dosage	Duration	Drug-drug interaction	Drug-disease/ conditions	Alternative medication
Beers 1991[12,14,15,18,35]	√	√		√	√			
Stuck criteria 1994[14,18]	√	√						
The geriatric medication algorithm 1994[12]	√			√		√	√	√
Oborne prescribing indicators 1997[12]	√	√		√		√		
Beers 1997[12,14,15,18,35]	√	√		√	√		√	
McLeod 1997[12,14,15,17–19,35,36]	√	√		√		√	√	√
Zhan criteria 2001[12,14,17–19,35,36]	√	√						
Fick-Beers 2003[12,14,15,18,19,35]	√	√		√	√		√	
Malon list of drug-drug interactions 2004[12,19]	√	√				√		
Rancourt criteria 2004[12,14,17–19,36]	√	√		√	√	√		
Lindblad 2006[12,14,15,17–19]							√	
Laroche 2007[12,14–18,35,36]	√	√		√		√	√	√
Winit-Watjan 2008[12,14–19,36]	√	√				√	√	
STOPP/START version 1 2008[12]	√	√	√	√	√	√	√	
APIT 2008[12,14–16,19,35]	√	√	√	√	√	√	√	
Portugal Beers criteria 2008[19]	√	√		√	√		√	√
Prescribing optimisation method for improving prescribing in the elderly 2009[12,15,36]	√	√	√	√	√	√	√	√
NORGEP 2009[12,14–19,35]	√	√		√		√		
FORTA 2009[12]	√	√						
PRISCUS 2010[12,14–19,36]	√	√		√				√
Kim 2010[14–19]	√	√		√	√	√	√	√
New Mexico criteria 2012[12,14,18]	√	√		√				√
Matanovic 2012[14–16,19,36]	√	√		√		√	√	√
Chang 2012[14–16,18,36]	√	√		√		√	√	√
Mann 2012[12,14–19,36]	√	√						√
Beers 2012[12,14,15,18]	√	√		√	√		√	√
APIT 2012[14,17,18,36]	√	√	√	√	√	√	√	
Clyne criteria 2013[14,18,19]	√	√		√	√	√	√	√
PIMHF 2014[15,17,19]	√	√					√	
RASP list 2014[14,17,36]	√	√		√	√	√	√	

TABLE 3 (Continued)

Tool name	Aspects of PIMs covered by the lists							
	PIMs independents of diagnosis	Stopping criteria	Starting criteria	Dosage	Duration	Drug-drug interaction	Drug-disease/ conditions	Alternative medication
FORTA 2014[14,16,18,19,36]	√	√	√	√				
High-risk medications 2015[19]	√						√	√
Beers 2015[14–16,18,36]	√	√		√	√	√	√	
Spanish adaptations of Beers criteria 2015[19]	√	√		√	√		√	√
EU (7)-PIM list 2015[14–16,18,19,36]	√	√		√	√			√
STOPP/START version 2 2015[14–19,41]	√	√	√	√	√	√	√	√
STOPP-START Spanish 2015[19]	√	√	√	√	√	√	√	√
Kim criteria 2015[14,16–19]	√	√		√		√	√	√
GheOP^{3}S 2016[14,18,36]	√	√	√	√	√	√	√	√
FORTA version 3 2018[17]	√	√		√			√	
EURO-FORTA 2018[17,19]	√	√		√				
Korean PIM 2018[17,19]	√	√		√	√	√	√	√
The updated PIM-Taiwan criteria 2019[17,19]	√	√		√	√		√	√
ES-PIA Project (Gonzalez criteria) 2019[17,19]	√	√		√		√	√	√
Beers 2019[14,17,19,41]	√	√		√	√	√	√	
Angular criteria 2019[19]	√	√					√	
Modified STOPP/START Sri Lanka 2019[19]	√	√	√	√	√	√	√	
Motter Brazilian consensus PIM 2019[19]	√	√		√	√		√	√
TIME 2020[17,19]/TIME 2021 validation study[19]	√	√	√	√	√	√	√	
US-FORTA 2020[17,19]	√	√		√				
JAPAN-FORTA 2020[17,19]	√	√		√	√			
STOPP Indonesia 2020[19]	√	√	√	√	√	√	√	
STOPPFall 2020[17]	√	√						
EU (7)-PIM list French 2020[19]	√	√		√	√	√		√
Hong Kong criteria 2021[17,19]	√	√		√	√	√	√	√
PIMHF 2021[17]	√	√		√				
GheOP3S version 2 2021[17,19]	√	√	√	√		√	√	
EU (7)-PIM criteria, Portugal 2021[19]	√	√		√	√			√
FORTA List 2021 2022[56]	√	√		√			√	
EURO-FORTA 2023[57]	√	√		√				
Beer 2023[58]	√	√		√	√	√	√	√
STOPP-version 3 2023[59]	√	√	√	√	√	√	√	√

TABLE 3 (Continued)

Tool name	Aspects of PIMs covered by the lists							
	PIMs independents of diagnosis	Stopping criteria	Starting criteria	Dosage	Duration	Drug-drug interaction	Drug-disease/ conditions	Alternative medication
PRISCUS 2023[60]	√	√		√				√
Tools developed to use for frail elderly with limited life expectancy/end-of-life								
Holmes, 2008[14,19,36,40]	√	√	√					
Patient-centred prescription model in elderly at the end of life 2015[40]		√		√		√	√	
OncPal deprescribing guideline 2015[19,41]	√	√						
NORGEP-NH 2015[14,15,17–19,36]	√	√		√	√	√		
Algorithm of medication review in frail older people 2016[19]	√	√		√				√
Futility criteria by Oliveira et al, 2016[41]		√					√	
MATCH-D 2016[17]		√					√	
LESS-CHRON 2017[40]		√					√	
STOPPFrail 2017[19,40]	√	√		√			√	
STOPP/START (United States) 2017[14,18,19]	√	√	√	√	√	√	√	
Morin European consensus criteria 2018[19]	√	√	√					
STOPPFrail 2021[17]	√	√		√	√		√	
Tools developed for use with special target groups								
The List of High-risk Perioperative Medications for Elders in China 2019[17,19]	√	√		√	√	√	√	√
PIM-Check 2017[14]	√	√	√	√	√	√	√	√
Explicit/mixed tools developed for use in children								
POPI 2011[39]	√	√	√	√	√	√	√	
POPI 2014[38,39]	√	√	√	√	√	√	√	
POPI 2016[39]	√	√	√	√	√	√	√	
Potentially inappropriate prescribing in children 2016[38,39]	√	√	√			√	√	
Modified POPI (UK) tool 2017 (short version),[38,39] modified POPI (UK) tool 2019 (full version)	√	√	√	√	√	√	√	
KIDs List 2020[38]	√	√		√	√			
POPI Int 2020[38]	√	√	√	√	√	√	√	

TABLE 3 (Continued)

Tool name	Aspects of PIMs covered by the lists							
	PIMs independents of diagnosis	Stopping criteria	Starting criteria	Dosage	Duration	Drug-drug interaction	Drug-disease/ conditions	Alternative medication
Implicit tools/tools with scoring systems								
MAI 1992[12,35,36]	Ten criteria (indication, effectiveness, dosage, correct directions, drug-drug interactions, drug-disease interactions, practical directions, costs, duplication, duration) worded as questions to assess the appropriateness of each prescribed drug with instructions for use and operational definitions for each criterion							
Lipton 1992[12]	Evaluation of each drug in the patient's regimen in seven categories of potential drug therapy problem. For each category a score of 0-9 is given							
Hamdy criteria for medication profile review in extended care 1995[12]	Aimed to reduce polypharmacy in patients in long-term care. Five open-ended questions assess the appropriates of patient medication, focusing on patients taking 10 or more medications							
Robertson's flow charts 1996[12]	Flow chart encouraging a uniform approach to preventing, identifying and correcting drug therapy problems							
Cantrill indicators of the appropriateness of long-term prescribing in general practice 1998[12]	Nine indicators of prescribing appropriateness for assessing the entire drug regimen of patients on long-term medications in general practice							
Barenholtz self-administered medication risk questionnaire in an elderly population 2003[12]	Ten-item questionnaire for use by elderly patients to help in identifying who is at increased risk of medication-related problems							
Sedative load 2003[36]	List of medicines with a proper or potential sedative effect (primary sedatives, drugs with sedation as a prominent side effect or preparations with a sedating component, drugs with sedation as a potential adverse effect). (Anticholinergic)							
Anticholinergic Risk Scale 2008[36]	Higher Anticholinergic Risk Scale scores were associated with increased risk of anticholinergic adverse effects in the geriatric evaluation and management cohort							
Comorbidity-polypharmacy score 2011[36]	Comorbidity-polypharmacy score was defined as the number of pre-admission medications plus comorbidities							
Implicit tools developed for use in frail elderly/limited life expectancy								
Holmes reconsidering MAI 2006[40]	Four components in a model of appropriate prescribing late in life: remaining life expectancy, time until benefit, goals of care, and treatment target							
Geriatric-palliative algorithm 2007[40]	Algorithm aimed at identifying whether a drug can be deprescribed based on indication, safety and alternative therapies							

Abbreviations: ACOVE-3, Assessing Care of Vulnerable Elders; APIT, Australian Prescribing Indicators Tool; EU, European Union; FORTA, Fit fOR The Aged; GP, general practitioner; LESS-CHRON, List of Evidence-based Deprescribing for Chronic Patients; LLE, limited life expectancy; MAI, medication appropriateness index; MATCH-D, Medication Appropriateness Tool for Comorbid Health Conditions in Dementia; PIM, potentially inappropriate medications; PIMHF, potentially inappropriate medication for heart failure; PPO, potential prescribing omission; RAND/UCLA, University of California at Los Angeles; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NORGEP, the Norwegian General Practice.

[a]Estonia, Finland, France, German, the Netherlands, Spain and Sweden.

[b]The UK, France, Spain, Italy, the Netherlands, Denmark, Czech Republic, Poland, Iceland, Belgium, Switzerland, Austria and Germany.

[c]The UK/Ireland, France, Poland, Italy, Spain, the Nordic countries and the Netherlands plus the original FORTA (Germany and Austria).

[d]Belgium, France, Germany, Italy, Norway, Portugal, Spain, Sweden, Switzerland and the UK.

[e]England, Belgium, Brazil, Canada, China, Ivory Coast, Ireland, Malaysia, Portugal, Switzerland, Turkey and Vietnam.

[f]Most of the tools use one of three rating scales: five-point Likert scale [1-5], nine-point Likert scale [1-9], 1 to 4 rating scale of FORTA-based tools. The decision to include the proposed medications/medication classes in the tools was based on the analysis of the experts' responses from the Likert scale. These tools used a median or mean score with 95% confidence interval (CI). The cut-off to classify the drug as a PIM slightly varied between tools (eg, EU (7)-PIM list classifies drugs as PIMs if both the mean value of the score and the upper limit of the 95% CI are lower than 3, whereas the updated PIM-Taiwan criteria, 2019 used a mean score of 3.5 as a cut-off.

2. *GRADE framework with consensus approach* ($n = 5/75$, 6.7%): The GRADE framework was integrated with the Delphi technique or the expert panel consensus approach to combine evidence-based decision-making and expert consensus. The GRADE approach facilitated a transparent and systematic evaluation of evidence and expert opinion and ensured a rigorous evaluation of evidence and expert input.[58,70,92,95,96]
3. *GRADE framework combined with consensus validation by the guideline development team* ($n = 8/75$, 10.7%): The GRADE framework was utilized along with consensus validation by the guideline development team. This combination allowed for evidence-based guidelines supported by a consensus of experts involved in the development process.[42–45,47–49,52]
4. *Consensus of guideline development team without the GRADE framework* ($n = 1$): In this approach, the guideline development team reached a consensus without using the GRADE framework for evidence evaluation. The team's expertise and consensus were the basis for the validation of the guidelines.[50]

3.4.2 | Metric-based validation techniques ($n = 3$)

This category involves validation methods that rely on metrics and measurements to assess the reliability and relevance of tools and guidelines, such as the psychometric test ($n = 1$),[120] the Content Validity Index method ($n = 1$),[84] and testing the tool in the field and comparing with expert panel decisions ($n = 1$).[81] The adaptation and translation of tools mainly employed the metrics approach, which focused on ensuring the reliability and relevance of the adapted or translated screening tools for identifying potentially inappropriate prescribing in older individuals.

3.4.3 | Panel size, rating scale, and percentage of agreement threshold

The consensus-based validation processes of the tools and guidelines showed variations in panel size, rating scales and consensus thresholds. The panel sizes involved in the validation of tools ranged from 4[99] to 57,[125] with the variation mainly influenced by whether multicounty or international experts were part of the process. On the other hand, the guideline development team consisted of nine to 12 members, who were responsible for developing the deprescribing guidelines.

In terms of rating scales, the review highlights the incorporation of different Likert rating scales such as [1-5], [1-9] and [1-10]. These diverse scales were used to assess the appropriateness of proposed medications or medication classes. Furthermore, the predefined percentage of agreement used to decide which medications or medication classes should be included in the tools or guidelines varied. For tools, a minimum agreement threshold of 60% was identified,[101] meaning that at least 60% of the experts needed to agree on the appropriateness of a medication or class for it to be included based on the median or mean scores. On the other hand, for guidelines, a minimum agreement threshold of 80% was set, requiring a substantial level of consensus among experts for a medication or class to be recommended in the guidelines.

3.5 | Medication lists developed by target populations

Applying the genealogy of tools (Figure 3) and conducting eligibility assessment Stage 3, we extracted medication data from 57.4% ($n = 35/66$) of validated explicit or mixed tools and all guidelines. Specifically, we selected 22 tools for adults aged 65 years and older with normal life expectancy,[56–60,64–66,83,88,89,93,111,113,114,126,128,129,131,133,147,148] two tools for very specific target groups (eg, perioperative patients),[74,121] four paediatric tools for patients under 18 years of age[63,67,70,73] and seven tools tailored to patients with limited life expectancy[62,81,101–103,123,124] (Figure 2).

The list of PIMs for persons aged 65 years and older with normal life expectancy and lists of medications for frail older persons with limited life expectancy are provided in Tables 4 and 5, respectively. However, to provide a more comprehensive resource for interested researchers and clinicians, we developed supporting files (Supporting Information Data S5). These files contain a comprehensive list of medications for each target population organized according to different aspects of appropriateness, ensuring that readers have access to detailed information for further exploration. A separate methodology outlining how we developed the medication lists is given in Supporting Information Data S2, offering valuable insights into the process. In the following section, we provide a comprehensive overview of the identified medications for each target population, highlighting key findings and essential details.

For persons aged 65 years and older with normal life expectancy, our analysis revealed 484 PIMs (437 medications and 47 medication classes) independent of diseases or conditions (Table 4), along with PIM lists for 54 diseases or conditions, 117 inappropriate omissions of medications,128 drug-drug interactions and 14 fall-risking medication classes. Moreover, 96 medications/medication classes were classified as having questionable benefits due to a lack of consensus among experts.

However, in our analysis, we found variations in the assignments of medications as PIMs, questionable benefit, or not PIMs across different tools. These variations were evident in the following ways:

1. A PIM in one tool is not a PIM in another tool, for instance rivaroxaban is considered a PIM in Beers 2023[58] but is not classified as a PIM in PRISCUS 2023.[60]
2. Some medications listed as a PIM in one tool were considered as having questionable benefits (no consensus) in another tool, for example phenylbutazone was reported as a PIM by the EU (7)-PIM list[126] and PRISCUS 2023,[60] but in Motter Brazilian consensus PIM 2019,[130] consensus was not reached.
3. In some cases, a drug classified as a PIM in one tool was listed as an alternative medication in another tool, for instance trazodone was categorized as a PIM by the Spanish tool (ES-PIA),[133] whereas

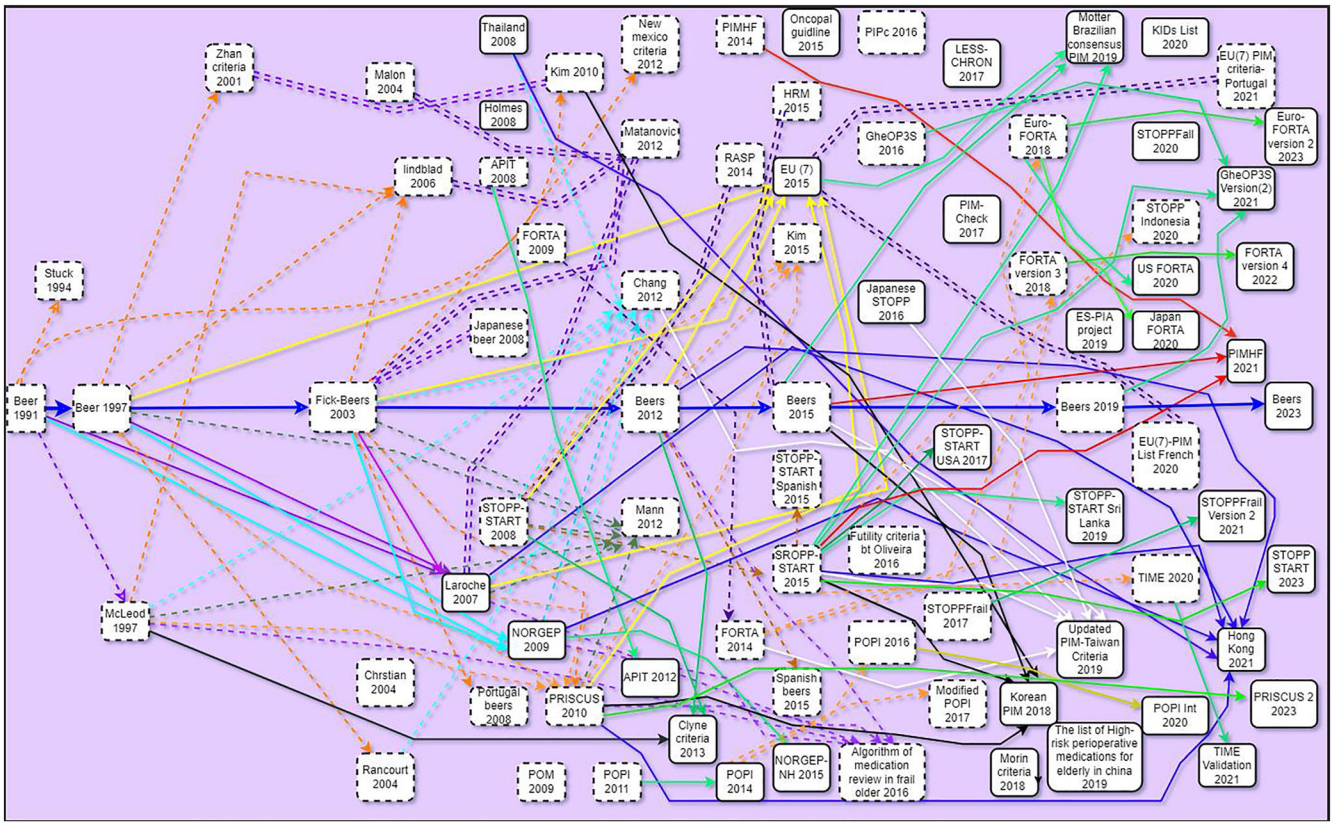

FIGURE 3 Genealogy-based selection of tools and guidelines for medication extractions. The identical version of the figure is available in the supporting information accompanying the manuscript. The version in the supporting information allows the option to enlarge the figure, enhancing its clarity and visibility (Supporting Information Data S2). Solid lines, arrow directed to selected tool included for medication extractions; single dotted lines, arrow directed to tools not included for medication extraction because no additional medications are provided; double dotted line, arrow directed to tools having additional medication listed but due to different reasons not selected for medication extraction (eg, not validated); centre blue line, links the Beers criteria; dotted rectangles, tools not included in medication extraction; solid line rectangles, tools included for medication extraction.

on the EU (7)-PIM list,[126] it was considered as an alternative treatment for dosulepin (classified as a PIM by EU (7)-PIM).

4. Daily dosage inconsistencies: The assignment of medications as PIMs was influenced by inconsistencies in the daily dosage criteria across different tools. For instance, lorazepam was classified as a PIM by Beers 2023[58] regardless of the dosage, whereas other tools specified particular dosages as PIMs, but the dosages were not standardized.[113,126,148]

For patients with limited life expectancy, the development of an integrated list of medications from different tools was challenging due to variations in frailty criteria, expected remaining life expectancy and the clinical components addressed (eg, the Holmes list was developed for advanced dementia, whereas STOPPFrail was developed generally for frail older persons with limited life expectancy). However, we identified a total of 202 (117 medication classes and 85 specific medications) items that were classified as either appropriate, inappropriate or questionable, depending on the clinical component addressed by the tools (Table 5).

The content of the tools primarily included a combination of appropriate/adequate medication lists and inappropriate/inadequate medications,[101,123] or provided PIM lists/deprescribing criteria alone.[62,81,102,103,124] The medications listed in these tools can be categorized as follows:

1. Adequate/appropriate medications prescribed for symptom management and comfort,[123] including analgesics (including opioids), antinauseants and drugs for constipation.
2. Inappropriate/inadequate drug treatments used for long-term prevention of chronic diseases, such as vitamin D and lipid-lowering medications (statins), which are targeted for deprescribing.[62,81,101,102,123,124]
3. Drugs with a questionable nature of the decision to continue or initiate treatments, such as digital glycosides, or those for which there is no consensus on use, such as fast-acting insulin, which may require patient-specific evaluation.[123]

For paediatric patients, we identified 152 potentially inappropriate prescriptions (PIPs), consisting of 78 that required clinical information and 74 criteria that could be applied in the absence of clinical information. Additionally, we found 29 potentially inappropriate

TABLE 4 Potentially inappropriate medication for persons aged 65 years and older with normal life expectancy.

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Alimentary tract and metabolism			
Drugs for acid-related disorders			
Antacids			
Magnesium hydroxide/antacids containing magnesium (>4 weeks)[60,126]	A02AA, A02AA04		
Aluminium-containing antacids[60,126]	A02AB, A02AD		
Drugs for peptic ulcer and gastro-oesophageal reflux disease			
H2-receptor antagonists[48,65,126]	A02BA	Moderate	Strong
Cimetidine[60,65,66,126,148]	A02BA01		
Ranitidine[65,126]	A02BA02		
Famotidine[60,65,126]	A02BA03		
Nizatidine[65]	A02BA04		
Proton-pump inhibitors (>8 weeks)[58–60,64,88,113,126,131]	A02BC	High: *C. difficile*, bone loss and fractures Moderate: pneumonia and gastrointestinal malignancies	Strong
Omeprazole[58,60]	A02BC01	High/moderate	Strong
Pantoprazole[58,60]	A02BC02	High/moderate	Strong
Lansoprazole[58,60]	A02BC03	High/moderate	Strong
Rabeprazole[58,60]	A02BC04	High/moderate	Strong
Esomeprazole[58,60]	A02BC05	High/moderate	Strong
Dexlansoprazole[58,60]	A02BC06	High/moderate	Strong
Drugs for functional bowel disorder			
Mebeverine[60,126]	A03AA04		
Trimebutine[126]	A03AA05		
Dicyclomine[58]	A03AA07	Moderate	Strong
Dihexyverine[126]	A03AA08		
Propantheline[89]	A03AB05		
Otilonium bromide[126]	A03AB06		
Tiemonium[126]	A03AB17		
Pinaveriumc[126]	A03AX04		
Atropine (excludes ophthalmic)[58,89]	A03BA01	Moderate	Strong
Hyoscyamine[58,88,126]	A03BA03	Moderate	Strong
Belladonna alkaloids[126,147,148]	A03BA04		
Homatropine (excludes ophthalmic)[58]	A03BB06	Moderate	Strong
Clidinium-chlordiazepoxide[58,65,66,126,148]	A03CA02	Moderate	Strong
Pitofenone[126]	A03DA02		
Metoclopramide[48,58,60,64,66,88,89,126,147]	A03FA01	Moderate	Strong
Domperidone (>30 mg/day)[60,126]	A03FA03		
Alizapride	A03FA05		
Antiemetics and antinauseants			
Scopolamine[126]	A04AD01		
Metopimazine[126,148]	A04AD05		
Drugs for constipation			
Viscous paraffin (liquid paraffin) Mineral oil, given orally[58,60,64,126]	A06AA01	Moderate	Strong
Docusate sodium[126,148]	A06AA02		

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Contact/stimulant laxatives[64,148]	A06AB		
Bisacodyl (>3 days)[64,126]	A06AB02		
Castor oil (= *Ricinus communis*, = Neoloid)[126,148]	A06AB05		
Senna glycosides (sennoside >1 week)[60,64,126]	A06AB06		
Cascara sagrada[126,148]	A06AB07		
Sodium picosulfate >1 week[60,64,126]	A06AB08		
Aloe[126,148]	A06AB13		
Prucalopride[126]	A06AX05		
Osmotically acting laxatives			
Magnesium oxide[48]	A06AD02	Low	Strong
Enema			
Sodium phosphate enema[89]	A06AG01		
Antidiarrheal, intestinal anti-inflammatory/ anti-infective agents			
Diphenoxylate-atropine[126]	A07DA01		
Loperamide (>3 day, >12 mg/day)[60,126]	A07DA03		
Racecadotril[126]	A07XA04		
Drugs used in diabetes			
Insulins and analogues			
Insulin, sliding scale (insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin)[48,58,66,126]		Moderate	Strong
Blood glucose-lowering drugs, excluding insulins			
Biguanides			
Buformin[48]	A10BA03	Low	Weak
Metformin[48]	A10BA02	Low	Weak
Sulfonylureas, long acting (type II diabetes mellitus)[48,58,59,64,65,88,89,113,131,148]	A10BB	High: hypoglycaemia Moderate: Cardiovascular events and all-cause mortality Low: Cardiovascular death and ischaemic stroke	Strong
Glyburide (glibenclamide)[48,58–60,65,66,113,126]	A10BB01	High/moderate/low	Strong
Chlorpropamide[48,59,65,113,126,147]	A10BB02		
Carbutamide[126,148]	A10BB06		
Glipizide[58,89,126,148]	A10BB07	High/moderate/low	Strong
Gliquidone[60]	A10BB08		
Gliclazide[58,60]	A10BB09	High/moderate/low	Strong
Glimepiride[58–60,126]	A10BB12	High/moderate/low	Strong
Thiazolidinediones	A10BG		
Pioglitazone[48,60,65,126]	A10BG03	High	Strong
α-Glucosidase inhibitors[48]	A10BF	Moderate	Weak
Acarbose[48,60,126]	A10BF01	Moderate	Weak
Miglitol[48]	A10BF02	Moderate	Weak

(Continues)

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Voglibose[48]	A10BF03	Moderate	Weak
Dipeptidyl peptidase 4 inhibitors	A10BH		
Sitagliptine[126]	A10BH01		
Vildagliptine[126]	A10BH02		
Sodium-glucose co-transporter 2 inhibitors (all)[48]	A10BK	Low	Strong
Blood and blood-forming organs			
Antithrombotic agents			
Vitamin K antagonists as first-line anticoagulant for atrial fibrillation[59]	B01AA		
Warfarin[58,147]	B01AA03	High	Strong
Acenocoumarol[126]	B01AA07		
Heparins and derivatives[133]	B01AB		
Platelet aggregation inhibitors excluding heparin[133]	B01AC		
Ticlopidine[59,60,66,88,126,147,148]	B01AC05		
Aspirin (long-term use at doses >100 mg/day)[59,88,131]	B01AC06		
Dipyridamole[64,88,126,148]	B01AC07	Moderate	Strong
Prasugrel[60,126]	B01AC22		
Cilostazol[60]	B01AC23		
Enzymes			
Alteplase[133]	B01AD02		
Direct thrombin inhibitors			
Dabigatran[59,126]	B01AE07		
Direct factor Xa inhibitors			
Rivaroxaban[58,126]	B01AF01	Moderate	Strong
Apixaban[59,126]	B01AF02		
Antianemic preparations			
Iron preparations (elemental iron doses >200 mg daily)[59,64,131]	B03A		
Ferrous fumarate[59,64,131]	B03AA02		
Ferrous gluconate[59,64,131]	B03AA03		
Ferrous sulphate[59,64,126,131]	B03AA07		
Cardiovascular system			
Cardiac therapy			
Cardiac glycosides			
Acetyldigoxin[60,126]	C01AA02		
Digitoxin[126]	C01AA04		
Digoxin[48,60,64–66,88,89,113,126,131,133,147,148] • First-line treatment of atrial fibrillation or heart failure[58] • Long-term (>3 months) use as a ventricular rate control[59]	C01AA05	Low: atrial fibrillation, heart failure Moderate: dosage >0.125 mg/day	Strong
Metildigoxin[126]	C01AA08		
Antiarrhythmics, classes I and III			
Antiarrhythmics, class Ia			
Quinidine[126]	C01BA01		

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Procainamide[126]	C01BA02		
Disopyramide[89,126,133,148]	C01BA03		
Quinidine in combination with verapamil[126]	C01BA51		
Antiarrhythmics, class Ib			
Lidocaine[60]	C01BB01		
Antiarrhythmics, class Ic			
Propafenone[60,126]	C01BC03		
Flecainide[60,66,126]	C01BC04		
Antiarrhythmics, class III			
Amiodarone[58,65,66,89,126]	C01BD01	High	Strong
Dronedarone[58,60,66,126]	C01BD07	High	Strong
Other cardiac preparations			
Trimetazidine[88,126]	C01EB15		
Ivabradine[126]	C01EB17		
Antihypertensive			
Antiadrenergic agents, centrally acting/ central alpha-agonists[58,59,64,88,89,131]	C02A	Low	Strong
Reserpine[64,88,126,131,148]	C02AA02		
Methyldopa[59,60,64,88,89,126,131,147]	C02AB01		
Clonidine[58–60,64,65,89,126,131,147,148]	C02AC01	Low	Strong
Guanfacine[58,59,64,126,131,148]	C02AC02	Low	Strong
Moxonidine[59,60,126,148]	C02AC05		
Rilmenidine[59,88,126,148]	C02AC06		
Guanabenz[64,131]		Low	Strong
Antiadrenergic agents, peripherally acting[48,58,65,66,89,147]	C02C	Moderate	Strong
Prazosin[58,65,66,89,126,147]	C02CA01	Moderate	Strong
Terazosin as antihypertensive[58,60,65,66,89,126]	G04CA03	Moderate	Strong
Doxazosin[58,60,65,66,89,126,147]	C02CA04	Moderate	Strong
Urapidil[48,126]	C02CA06	Moderate	Strong
Guanethidine[126]	C02CC02		
Agents acting on arteriolar smooth muscle			
Dihydralazine[60]	C02DB01		
Hydralazine[60,126]	C02DB02		
Minoxidil[60]	C02DC01		
Diuretics			
Loop diuretics[48]		Moderate	Strong
Loop diuretic as: • First-line treatment for hypertension[59,131] • For dependent ankle oedema[59,88,131]	C03C		
Potassium-sparing agent[65]	C03D	Moderate	Strong
Spironolactone (>25 mg/day)[65]	C03DA01	Moderate	Strong
Eplerenone[48]	C03DA04	Moderate	Strong

(Continues)

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Peripheral vasodilators			
Pentoxifylline[60,126,148]	C04AD03		
Ergoloid mesylates[58,126,147,148]	C04AE01	High	Strong
Nicergoline[60,126,148]	C04AE02		
Dihydroergocristine[126,148]	C04AE04		
Raubasine-dihydroergocristine[126,148]	C04AE54		
Cyclandelate (cyclospasmol)[126]	C04AX01		
Vincamine[126,148]	C04AX07		
Moxisylyte[126,148]	C04AX10		
Vinburnine[126,148]	C04AX17		
Buflomedil[126]	C04AX20		
Naftidrofuryl[60,126,148]	C04AX21		
Vasoprotectives			
Hidrosmin[126]	C05CA05		
Escin (= aescin)[126]	C05CA07		
Vincamine-rutoside[126,148]	C05CA51		
Troxerutin-vincamine[126,148]	C05CA54		
Beta-blocking agents			
Oxprenolol[126]	C07AA02		
Pindolol[60,126]	C07AA03		
Propranolol[60,126]	C07AA05		
Sotalol[60,111,126,133]	C07AA07		
Nadolol[126]	C07AA12		
Labetalol[126]	C07AG01		
Calcium channel blockers			
Selective calcium channel blockers with mainly vascular effects[58,65,66,89,126,147]	C08C	Moderate	Strong
Nicardipine[126,148]	C08CA04		
Nifedipine[89,147]	C08CA05	Moderate	Strong
• Non-sustained/immediate release[58,60,126,148] sustained/extended-release[126]			
• Nimodipine[60]	C08CA06		
Selective calcium channel blockers with direct cardiac effects			
Verapamil[126,147]	C08DA01		
Diltiazem[126]	C08DB01		
Agents acting on the renin-angiotensin system			
Aliskiren[60]	C09XA02		
Lipid modifying agents			
Niacin (= nicotinic acid)[126]	C10AD02		
Genito-urinary system and sex hormones			
Sex hormones and modulators of the genital system			
Androgens[58,65,89,131]	G03B	Moderate	Weak
Methyltestosterone[58,65,131]	G03BA02	Moderate	Weak

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Testosterone[58,60,65,89,131,147]	G03BA03	Moderate	Weak
Estrogens (including combination)[58,60,65,66,147]	G03C	High: oral and patch Moderate: vaginal cream or vaginal tablet	Strong: oral and patch strong Weak: topical vaginal cream or tablets
Estradiol[65,89]	G03CA03		
Estriol[65]	G03CA04		
Tibolone[65,89]	G03CX01		
Estrone[65]	G03CA07		
Estradiol, combinations[65]	G03CA53		
Conjugated estrogens[65]	G03CA57		
Progesterone and estrogen[65]	G03FA04		
Norethisterone and estrogen[65]	G03FA01		
Hydroxyprogesterone and estrogen[65]	G03FA02		
Norgestrel and estrogen[65]	G03FA10		
Medroxyprogesterone and estrogen[65]	G03FA12		
Urologicals			
Drugs for urinary frequency and incontinence[48]	G04BD	High	Strong
Flavoxate[60]	G04BD02		
Transdermal oxybutynin[48]	G04BD04	High	Strong
Oxybutynin[48,58,60,65,66,126,147,148]	G04BD04	High	Strong
Propiverine hydrochloride[48,60]	G04BD06	High	Strong
Tolterodine[48,60,65,126,148]	G04BD07	High	Strong
Solifenacin[48,60,126,148]	G04BD08	High	Strong
Trospium[60,126]	G04BD09		
Darifenacin[60,126]	G04BD10		
Fesoterodine[48,60,126]	G04BD11	High	Strong
Desfesoterodine[60]	G04BD13		
Imidafenacin[48]	G04BD14	High	Strong
Mirabegron[60]	G04BD12		
Duloxetine with urinary urgency or urge incontinence[59]	N06AX21		
Systemic hormonal preparations, excluding sex hormones and insulins			
Growth hormone[58,66]	H01AC01	High	Strong
Vasopressin[59]	H01BA01		
Desmopressin[58–60,64,66]	H01BA02	Moderate	Strong
Levothyroxine[147]	H03AA01		
Teriparatide[88]	H05AA02		
Desiccated thyroid[58]		Low	Strong
Anti-infective for systematic use			
Fluoroquinolones[60]	J01MA		
Ofloxacin[60,126]	J01MA01		
Ciprofloxacin[60]	J01MA02		
Norfloxacin[60]	J01MA06		
Levofloxacin[60]	J01MA12		
Moxifloxacin[60]	J01MA14		
Aminoglycosides[147]	J01G		

(Continues)

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Nitrofurantoin[58,64,83,89,126,148]	J01XE01		
Hexamine (methenamine)[83]	J01XX05		
Antineoplastic and immunomodulating agents			
Medroxyprogesterone[60]	L02AB02		
Megestrol acetate[58,59,88]	L02AB01		
Musculo-skeletal system			
Anti-inflammatory and anti-rheumatic products			
Anti-inflammatory and anti-rheumatic products, NSAIDs[64]			
Non-COX-2-selective NSAIDs, oral[48,58,60,66,89,126,130,147]		Moderate[58] High[48]	Strong
Phenylbutazone[60,89,126,147,148]	M01AA01		
Indomethacin[58,60,65,66,89,126,130,148]	M01AB01	Moderate	Strong
Sulindac[58,65,89]	M01AB02	Moderate	Strong
Tolmetin[65,66]	M01AB03		
Diclofenac[58,60,65,66,89,126,130]	M01AB05	Moderate	Strong
Alclofenac[89]	M01AB06		
Etodolac[58,65,130]	M01AB08	Moderate	Strong
Acemetacin[60,65]	M01AB11		
Proglumetacin[60]	M01AB14		
Ketorolac, includes oral and parenteral[58,65,66,89,126,130]	M01AB15	Moderate	Strong
Aceclofenac[58,60,65,89,130]	M01AB16	Moderate	Strong
Piroxicam[58,60,65,66,89,126,130,147]	M01AC01	Moderate	Strong
Tenoxicam[58,65,89,130]	M01AC02	Moderate	Strong
Lornoxicam[58,89,126,130]	M01AC05	Moderate	Strong
Meloxicam[58,60,65,89,126,130]	M01AC06	Moderate	Strong
Ibuprofen[58,60,65,66,89,126,130]	M01AE01	Moderate	Strong
Naproxen[58,60,66,89,126,130,147]	M01AE02	Moderate	Strong
Ketoprofen[60,65,126,130]	M01AE03		
Fenoprofen[65]	M01AE04		
Fenbufen[65]	M01AE05		
Flurbiprofen[58,65,89,126,130]	M01AE09	Moderate	Strong
Tiaprofenic acid[65]	M01AE11		
Oxaprozin[58]	M01AE12	Moderate	Strong
Dexibuprofen[66]	M01AE14		
Dexketoprofen[60,126]	M01AE17		
Mefenamic acid[65,66,89,126,130]	M01AG01		
Flufenamic acid[65]	M01AG03		
Nabumetone[58,60,65,126]	M01AX01	Moderate	Strong
Niflumic acid[65]	M01AX02		
Benzydamine[65]	M01AX07		
Nimesulide[58,65,89,130]	M01AX17		
COX II inhibitors (coxibs)[60,89,126,130,147]			
Celecoxib[48,60,89,126,130,147]	M01AH01	High	Strong
Etoricoxib[60,89,126,130,147]	M01AH05		

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Anti-inflammatory preparations non-steroids for topical use	M02A		
Etofenamate[60]	M02AA06		
Loxoprofen (topical use)[89,130]	M02AA31		
Muscle relaxants	M03		
Muscle relaxants, centrally acting agents[58,66,88,89,126,130]	M03B	Moderate	Strong
Carisoprodol[58,88,111,126,130,147]	M03BA02	Moderate	Strong
Chlorzoxazone[58,88]	M03BB03	Moderate	Strong
Cyclobenzaprine[58,88,126,130]	M03BX08	Moderate	Strong
Metaxalone[58,88]		Moderate	Strong
Methocarbamol[58,60,66,88,126,147,148]	M03BA03	Moderate	Strong
Orphenadrine[58,60,66,88,89,126,130,147]	M03BC01	Moderate	Strong
Tolperisone[60]	M03BX04		
Thiocolchicoside[88,130]	M03BX05		
Tizanidine[60,88,126]	M03BX02		
Baclofen[60,89,126,130,148]	M03BX01		
Pridinol[60]	M03BX03		
Tolperisone[60,89]	M03BX04		
Tetrazepam[126,148]	M03BX07		
Chlorfenese[88]			
Antigout preparations			
Allopurinol for asymptomatic hyperuricemia (those without gout or nephrolithiasis)[88]	M04AA01		
Colchicine[126]	M04AC01		
Drugs affecting bone structure and mineralization			
Bisphosphonates for >5 years[64]	M05BA		
Zoledronate[88]	M05BA08		
Strontium ranelate[126]	M05BX03		
Denosumab[88]	M05BX04		
Other drugs for disorders of the musculo-skeletal system			
Quinine and derivatives[60,126]	M09AA		
Nervous system			
Anesthetics			
Propofol[133]	N01AX10		
Benzocaine[133]	N01BA05		
Topical lidocaine (lignocaine) patch for treatment of chronic osteoarthritis pain[59]	N01BB02		
Analgesics			
Opioids[64,66]			
Pethidine (meperidine)[58,60,64,66,88,126,130,133,147]	N02AB02	Moderate	Strong
Pentazocine[64,66,126]	N02AD01		
Tramadol (sustained-/non-sustained-release)[60,126,130]	N02AX02		

(Continues)

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Tapentadol[60]	N02AX06		
Morphine[133]	N02AA01		
Dihydrocodeine[60]	N02AA08		
Codeine[60]	R05DA04		
Polyethylene glycol electrolyte powder[89]	N02AA59		
Dextropropoxyphene[111]	N02AC04		
Oral or transdermal strong opioids as first-line therapy for mild pain[59,131]			
Other analgesics and antipyretics			
Acetylsalicylic acid (>325 mg)[58,60,64,66,113,126,130,133]	N02BA01	Moderate	Strong
Diflunisal[58]	N02BA11	Moderate	Strong
Phenazone[60]	N02BB01		
Propyphenazone[60]	N02BB04		
Long-term opioids for osteoarthritis[59]			
Gabapentinoids for non-neuropathic pain[59]	N02BF		
Gabapentin[59]	N02BF01		
Gregabalin[59]	N02BF02		
Antimigraine preparations			
Ergotamine[60,126]	N02CA02		
Triptanes[126]	N02CC		
Sumatriptan[126]	N02CC01		
Naratriptan[126]	N02CC02		
Zolmitriptan[126]	N02CC03		
Eletriptan[126]	N02CC06		
Antiepileptics			
Phenobarbital[58,60,88,126,147]	N03AA02	High	Strong
Primidone[58,60]	N03AA03	High	Strong
Phenytoin[60,88,126]	N03AB02		
Clonazepam[58,65,66,126]	N03AE01	Moderate	Strong
Carbamazepine[60,88,126,133]	N03AF01		
Oxcarbazepine[133]	N03AF02		
Topiramate[126]	N03AX11		
Gabapentin[133]	N03AX12		
Valproate[88]	N03AG01		
Anti-Parkinson drugs			
Anticholinergic agents to treat extra-pyramidal side-effects of neuroleptic medications			
Trihexyphenidyl[48,58–60,65,66,126]	N04AA01	Moderate	Strong
Biperiden[48,59,60,65,126]	N04AA02	Moderate	Strong
Procyclidine[59,60]	N04AA04		
Bornaprine[60]	N04AA11		
Tropatepin[126]	N04AA12		
Orphenadrine[59]	N04AB02		
Benztropine (oral)[58,66,126]	N04AC01	Moderate	Strong
Dopaminergic agents	N04B		

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Amantadine[60,126]	N04BB01		
Bromocriptine[126]	N04BC01		
Pergolide[60,126]	N04BC02		
Dihydroergocryptine[60,126]	N04BC03		
Ropinirole[126]	N04BC04		
Pramipexole[60,126]	N04BC05		
Cabergoline[126]	N04BC06		
Piribedil[60,126]	N04BC08		
Rotigotine[126]	N04BC09		
Selegiline[60,126]	N04BD01		
Tolcapone[60,126]	N04BX01		
Levodopa or dopamine agonists for benign essential tremor or for treatment of extrapyramidal side-effects of antipsychotics or other forms of drug-induced Parkinsonism[59,88,131]	N04BA01/ N04BC		
Psycholeptics			
Antipsychotics[58,64–66,89,111,126,133,147,148]		Moderate	Strong
Chlorpromazine[58,66,89,111,126,147,148]	N05AA01	Moderate	Strong
Levomepromazine[60,65,111,126,148]	N05AA02		
Cyamemazine[126,148]	N05AA06		
Fluphenazine[58,60,65,126,133,148]	N05AB02	Moderate	Strong
Perphenazine[58,60,65,126,148]	N05AB03	Moderate	Strong
Prochlorperazine[48,89,111,126]	N05AB04	Moderate	Strong
Trifluoperazine[65,89,126]	N05AB06		
Perazine[60]	N05AB10		
Propericiazine/periciazine/ pericyazine[126,148]	N05AC01		
Thioridazine[60,65,126]	N05AC02		
Pipotiazine[126,148]	N05AC04		
Haloperidol (>2 mg single dose, >5 mg/day)[58,60,65,66,89]	N05AD01	Moderate	Strong
Melperone (>100 mg/day, >6 weeks[60])	N05AD03		
Pipamperone (>120 mg/day, >6 weeks[60])	N05AD05		
Bromperidol[60]	N05AD06		
Benperidol[60]	N05AD07		
Droperidol[126]	N05AD08		
Sertindole[60,126]	N05AE03		
Ziprasidone[58,60,65,89,126]	N05AE04	Moderate	Strong
Lurasidone[58,65]	N05AE05	Moderate	Strong
Flupentixole[60,65,126]	N05AF01		
Chlorprothixene[60,65,111,126]	N05AF03		
Zuclopenthixol[60,126]	N05AF05		
Fluspirilene[60]	N05AG01		
Pimozide[60,65,89,126,133]	N05AG02		
Loxapine[65]	N05AH01		
Clozapine[58,60,65,66,89,126,147]	N05AH02	Moderate	Strong
	N05AH03	Moderate	Strong

(Continues)

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Olanzapine (>10 mg/day)[58,60,65,66,89,126,147]			
Quetiapine (>100 mg/day, >6 weeks)[58,60,66,89]	N05AH04	Moderate	Strong
Sulpiride[48,60,65]	N05AL01	Low	Strong
Tiapride[60]	N05AL03		
Amisulpride[60,65]	N05AL05		
Lithium[126,133]	N05AN01		
Prothipendyl[60]	N05AX07		
Risperidone (>6 weeks)[58,60]	N05AX08	Moderate	Strong
Zotepine[65]	N05AX11		
Aripiprazole[58,60,65,89,126]	N05AX12	Moderate	Strong
Paliperidone[58,60,65,89]	N05AX13	Moderate	Strong
Cariprazine[58,60]	N05AX15	Moderate	Strong
Brexpiprazole[58]	N05AX16	Moderate	Strong
Pimavanserin[58]	N05AX17	Moderate	Strong
Benzodiazepines[48,58–60,64,66,83,88,113,131,133,147]	N05BA/ N05CD	Moderate[58] High[48]	Strong
Short and intermediate acting			
Oxazepam[58,60,65,113,126,148]	N05BA04	Moderate	Strong
Lorazepam[58,60,65,66,89,113,126,147,148]	N05BA06	Moderate	Strong
Alprazolam[58,60,65,66,89,113,126,147,148]	N05BA12	Moderate	Strong
Clotiazepam (>5 mg/day)[126,148]	N05BA21		
Estazolam[58,65,126]	N05CD04	Moderate	Strong
Triazolam[48,58,60,65,66,89,113,126,147,148]	N05CD05	Moderate	Strong
Lormetazepam[60,126,148]	N05CD06		
Temazepam[58,60,66,113,126,148]	N05CD07	Moderate	Strong
Midazolam[58,65,89,126]	N05CD08	Moderate	Strong
Brotizolam[60,65,126]	N05CD09		
Loprazolam (>0.5 mg)[126,148]	N05CD11		
Long acting			
Diazepam[48,58,60,65,66,89,111,113,126,147,148]	N05BA01	Moderate[58] High[48]	Strong
Chlordiazepoxide[58,60,66,89,113,126,147,148]	N05BA02	Moderate	Strong
Chlordiazepoxide combined with amitriptyline[58]	N05BA02	Moderate	Strong
Chlordiazepoxide combined with clidinium[58]	N05BA02	Moderate	Strong
Medazepam[60,65,126]	N05BA03		
Clorazepate (dipotassium clorazepate)[58,60,113,126,148]	N05BA05	Moderate	Strong
Lorazepate-acepromazine[126,148]	N05BA05		
Aceprometazine[126,148]			
Bromazepam[65,66,89,126,148]	N05BA08		
Clobazam[58,65,66,89,126,148]	N05BA09	Moderate	Strong
Prazepam[65,126,148]	N05BA11		
Halazepam[126]	N05BA13		
Nordazepam[65,126,148]	N05BA16		

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Fludiazepam[65]	N05BA17		
(Ethyl-)loflazepate[126,148]	N05BA18		
Etizolam[48,148]	N05BA19	High	Strong
Flurazepam[48,58,65,66,113,126,147]	N05CD01	High	Strong
Nitrazepam[65,89,111,126,148]	N05CD02		
Flunitrazepam[65,66,89,111,126,148]	N05CD03		
Quazepam[126]	N05CD10		
Loprazolam[126,133]	N05CD11		
Oxazolam[65,111]			
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, Z-drugs)[48,58,59,64,65,88,89,131]	N05CF	Moderate	Strong
Zopiclone[48,60,65,88,89,111,126,148]	N05CF01	Moderate	Strong
Zolpidem[48,58,60,65,66,88,89,126,148]	N05CF02	Moderate	Strong
Zaleplon[58,65,88,126]	N05CF03	Moderate	Strong
Eszopiclone[48,58,65]	N05CF04	Moderate	Strong
Hydroxyzine[58,60,65,66,89,111,133,148]	N05BB01	Moderate	Strong
Carbamate[88]	N05BC		
Meprobamate[58,126]	N05BC01	Moderate	Strong
Barbiturates[64]	N05CA		
Butalbital[58]	N05CB01	High	Strong
Chloral hydrate[60,126]	N05CC01		
Other hypnotics and sedatives			
Clomethiazole[60,126]	N05CM02		
Propiomazine[126]	N05CM06		
Psychoanaleptics			
Antidepressants, alone or in combination[58,64,66,147,148]	N06A		
Non-selective monoamine reuptake inhibitors (Tricyclic Antidepressants)[48,58–60,88,147]	N06AA	High	Strong
Desipramine[58,126]	N06AA01	High	Strong
Imipramine[48,58,60,65,89,126,133,147,148]	N06AA02	High	Strong
Clomipramine[48,58,60,65,89,111,126,133,148]	N06AA04	High	Strong
Opipramol[60]	N06AA05		
Trimipramine[60,89,111,126,148]	N06AA06		
Amitriptyline[58,60,65,89,111,126]	N06AA09	High	Strong
Nortriptyline[58,60,89,126]	N06AA10	High	Strong
Doxepin (>6 mg/day)[58,60,65,89,111,126,147,148]	N06AA12	High	Strong
Dosulepin[126,148]	N06AA16		
Amoxapine[58,126]	N06AA17	High	Strong
Maprotiline[60,65,126,148]	N06AA21		
Selective serotonin reuptake inhibitors[58,88]	**N06AB**	High	Strong
Fluoxetine[60,88,126]	N06AB03		
Escitalopram >10 mg/day[88]	N06AB04		
Paroxetine[58,60,65,88,126]	N06AB05	High	Strong
Sertraline >100 mg/day[60]	N06AB06		

(Continues)

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Fluvoxamine[60,88,126]	N06AB08		
Citalopram >20 mg/day[88]	N06AB10		
Monoamine oxidase inhibitors			
Tranylcypromine[60,126]	N06AF04		
Moclobemide[60]	N06AG02		
St John's wort[60]			
Other antidepressants			
Mianserin[60]	N06AX03		
Trazodone[133]	N06AX05		
Mirtazapine[133]	N06AX11		
Bupropion[60,126]	N06AX12		
Tianeptine[60]	N06AX14		
Venlafaxine[126]	N06AX16		
Reboxetine[126]	N06AX18		
Agomelatine[60]	N06AX22		
Psychostimulants, agents used for Attention deficit hyperactivity disorder and nootropics			
Methylphenidate[60,126,133]	N06BA04		
Pyritinol[60]	N06BX02		
Piracetam[60,88,126,148]	N06BX03		
Antidepressants in combination with psycholeptics			
Melitracen and psycholeptics[65]	N06CA02		
Anti-dementia drugs			
Ginkgo biloba/Ginkgo folium[60,126,148]	N06DX02		
Parasympathomimetics			
Bethanechol[126]	N07AB02		
Drugs used in addictive disorders			
Methadone[60,126]	N07BC02		
Levomethadone[60]	N07BC05		
Antivertigo			
Betahistine[60,88]	N07CA01		
Cinnarizine[60,147]	N07CA02		
Flunarizine[60,147]	N07CA03		
Respiratory system			
Intranasal decongestants >10 days (decongestants and other nasal preparations for topical use)[64]	R01A		
Nasal decongestants for systemic use (sympathomimetics)[64,126,133]			
Norephedrine (phenylpropanolamine)[126]	R01BA01		
Pseudoephedrine[126]	R01BA02		
Phenylephrine[64,133]	R01BA03		
Drugs for obstructive airway diseases	R03		
Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD[59,88,113,131]			

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Sympathomimetics for systemic use, no inhalation[60,126]	R03CC		
Salbumatol[60]	R03CC02		
Terbutaline[60,126]	R03CC03		
Bambuterol[60]	R03CC12		
Clenbuterol[60]	R03CC13		
Reproterol[60]	R03CC14		
Other systemic drugs for airway diseases			
Theophylline[59,60,64,88,111,113,126,131,147]	R03DA04		
Aminophylline[60]	R03DA05		
Cough and cold preparations	**R05**		
Opium alkaloids and derivatives[64]	R05D		
Ethylmorphine[126]	R05DA01		
Codeine[60,126]	R05DA04		
Dihydrocodeine[60]	N02AA08		
Dextrometorphan[126]	R05DA09		
Antihistamines, systemic use			
First generation[48,58,59,64–66,89,113,131,133]		Moderate	Strong
Brompheniramine[58,148]	R06AB01	Moderate	Strong
Brompheniramine, combinations[65]	R06AB51		
Triprolidine, combinations[65,148]	R06AX07		
Promethazine, combinations[65]	R06AD52		
Promethazine[48,60,65,89,111,113,126,148]	R06AD02	Moderate	Strong
Dexchlorpheniramine, combinations (dexchlorpheniramine-betamethason)[65,126,148]	R06AB52		
Dexchlorpheniramine[65,89,111,126,148]	R06AB02		
Diphenhydramine[48,58,60,65,66,89,113,148]	R06AA02	Moderate	Strong
Dimenhydrinate[58,60,65,66,126,148]	R06AA11	Moderate	Strong
Clemastine[60,65,126]	R06AA04		
Diphenylpyraline[65]	R06AA07		
Carbinoxamine[65,126,148]	R06AA08		
Doxylamine[58,60,65,126,148]	R06AA09	Moderate	Strong
Trimethobenzamide[88]	R06AA10		
Diphenhydramine, combinations[65]	R06AA52		
Diphenylpyraline, combinations[65]	R06AA57		
Brompheniramine[25,65]	R06AB01		
Chlorpheniramine (chlorphenamine)[48,58,65,66,89,113,126,148]	R06AB04	Moderate	Strong
Mequitazine[65,126,148]	R06AD07		
Oxomemazine[126,148]	R06AD08		
Buclizine[65,126,148]	R06AE01		
Cyclizine[65,113,126]	R06AE03		
Chlorcyclizine[65]	R06AE04		
Meclizine (meclozine)[58,65,126,148]	R06AE05	Moderate	Strong
Oxatomide[65]	R06AE06		
Buclizine, combinations[65]	R06AE51		

(Continues)

TABLE 4 (Continued)

Organ system	ATC code[a]	Quality of evidence[b]	Strength of recommendation[c]
Meclizine, combinations[65]	R06AE55		
Homochlorcyclizine HCl (homoginin)[65]	R06AE91		
Cyproheptadine[58,60,65,89,126,148]	R06AX02	Moderate	Strong
Phenindamine[65]	R06AX04		
Triprolidine[48,58,65,66,126,148]	R06AX07	Moderate	Strong
Mebhydrolin[65]	R06AX15		
Pimethixene[126,148]	R06AX23		
Ketotifen[60,65]	R06AX17		
Pheniramine[126,148]	R06AB05		
Trimeprazine (alimemazine)[126,148]	R06AD01		
Dimetindene[60,126]	R06AB03		
Tripelennamine[126]	R06AC04		
Second generation antihistamine			
Terfenadine[126]	R06AX12		
Ebastine[60,126]	R06AX22		
Rupatadine[60]	R06AX28		

Abbreviations: ATC, Anatomical Therapeutic Chemical.
[a]If the medication had no ATC code, this field was left blank.
[b]The quality of evidence was not graded by us; rather, it was directly assigned based on information taken from the original articles, specifically the Beer 2023 criteria and the Screening Tool for Older Persons' Appropriate Prescriptions for Japanese (STOPP Japanese 2016). If any discrepancies were identified, they were specified. If the quality of evidence is not filled in, this indicates that the medications were not included in the two tools.
[c]Similar to the quality of evidence, the strength of evidence was also based on the reports from the articles.

omissions (PIOs) for the treatment of commonly encountered health problems in all or subgroups of paediatric patients (Supporting Information Data S5).

3.6 | Medication evidence levels included in tools and guidelines

Among the 35 tools and nine guidelines selected for medication extractions, only two tools (one for older persons with normal life expectancy and one for paediatric patients) and eight guidelines following the GRADE framework provided information on the level of evidence for reported medications (Figure 2). For older persons with limited life expectancy, none of the tools offered a level of evidence. For older adults aged 65 years and above, Beers 2023 tools[58] and Japanese STOPP 2016 guidelines[48] provided information on the level of evidence and strength of recommendations for medications in their lists. Approximately 7.4% of medications in Beers 2023 tools ($n = 242$) were supported by low-quality evidence, 71.5% by moderate-quality evidence and 21.1% by high-quality evidence. The Japanese STOPP 2016 guidelines ($n = 37$) had 10.8% recommendations backed by low-quality evidence, 40.5% by intermediate-quality evidence and 48.6% by high-quality evidence. Notably, there was a discrepancy observed, particularly concerning medications such as benzodiazepine and non-steroidal anti-inflammatory drugs, both listed as PIMs but with different levels of quality of evidence for avoiding their use in older persons (Table 4). Compiling the two tools for older persons, approximately a quarter (24.7%, $n = 69/279$) of medications were included based on a high quality of evidence. The evidence available for paediatric patients was also limited, with only the KIDs list providing information on the quality of evidence. About 47.9% of the list's contents were supported by low and very low-quality evidence, while 19.7% and 32.4% were backed by moderate- and high-quality evidence, respectively ($n = 71$). Detailed information on the level of evidence for medications can be found in Supporting Information Data S5.

4 | DISCUSSION

In this umbrella review, including 15 systematic reviews, we identified 72 explicit and 12 mixed tools for medication appropriateness assessment, along with nine guidelines for deprescribing. A significant proportion of explicit/mixed tools ($n = 66/84$, 78.57%) and all guidelines were validated, with the (modified) Delphi technique being the most common validation approach ($n = 58/75$, 77.3%). We developed a comprehensive list of medications, including 484 PIMs for older adults with a normal life expectancy, along with lists for 54 diseases/conditions, 128 drug-drug interactions and 96 drugs with questionable benefits. Additionally, we identified 117 medication classes and 85 specific medications for older persons with limited life expectancy, categorized based on their appropriateness with different clinical

TABLE 5 Overview of potentially inappropriate medications in frail patients with limited life expectancy eligible for deprescribing

Medication/medication class	ATC code	STOPPFrail 2021[62a]	Morin 2018[123b]	
Definition of frailty with limited life expectancy		Frail older adults with less than 1 year of life remaining	Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
			Initiation	Continuation
Alimentary tract and metabolism				
Drugs for acid-related disorders, excluding PPIs			Questionable	Questionable
H2 receptor antagonist	A02BA	PIM		
Proton pump inhibitors	A02BC	PIM	No consensus	No consensus
Antispasmodics	A03			
Butylscopolamine	A03BB01		Often adequate	Often adequate
Metoclopramide	A03FA01		Often adequate	No consensus
Antiemetics and antinauseants	A04A		Often adequate	Often adequate
Drugs for constipation/laxatives	A06A		Often adequate	Often adequate
Antidiarrheal	A07DA			
Antidiabetic drugs	A10	PIM		
Insulin	A10A			
Fast-acting insulin	A10AB		No consensus	No consensus
Intermediate-acting insulin	A10AC		Questionable	No consensus
Combined insulin	A10AD		Questionable	No consensus
Long-acting insulin	A10AE		No consensus	No consensus
Oral diabetic agents	A10B		Questionable	
Other oral antidiabetics, excluding metformin				Questionable
Metformin	A10BA02			No consensus
Sulfonylureas	A10BB			Questionable
Acarbose	A10BF01			
Thiazolidinediones	A10BG			
Dipeptidyl peptidase 4 inhibitors	A10BH			
Glucagon-Like Peptide-1 analogues	A10BJ			
Vitamins	A11			
Multivitamin combination supplements	A11A	PIM		
Vitamin D	A11CC		Often inadequate	Often inadequate
Minerals	A12			
Calcium supplement	A12A		Often inadequate	Often inadequate

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	ATC code	STOPPFrail 2021[62a] Frail older adults with less than 1 year of life remaining	Morin 2018[123b] Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
			Initiation	Continuation
Nutritional supplements (other than vitamins)		PIM		
Complementary-alternative medicines				
Appetite stimulants				
Blood and blood-forming organs				
Vitamin K antagonists	B01AA		Often inadequate	Questionable
Warfarin	B01AA03			
Unfractionated heparin	B01AB01		Questionable	Questionable
Low molecular weight heparin	(B01AB04 - B01AB11)		Questionable	No consensus
Platelet aggregation inhibitors	B01AC	PIM	Questionable	
Antiplatelet agents, excluding aspirin	B01AC			Questionable
Aspirin	B01AC06	PIM		Questionable
Oral anticoagulants				
Novel oral anticoagulants	B01AE, B01AF		Often inadequate	Questionable
Other anticoagulants	B01AD, B01AX		Often inadequate	Questionable
Antianaemic preparations	B03			Questionable
Iron	B03AA			
Oral elemental iron doses >200 mg/day				
Iron preparations and erythropoietin	B03A, B03XA01		Often inadequate	
Vitamin B12 and folic acid	B03B		Often inadequate	
Folic acid	B03BB01	PIM		
Red blood cell colony stimulating factors	B03XA			
Blood products	B05A		Questionable	Questionable
Electrolytes	B05XA			
Cardiovascular system				
Digitalis glycosides	C01AA		Questionable	Questionable
Digoxin	C01AA05			
Cardiac glycosides, excluding digoxin	C01A		Often inadequate	Questionable
Antiarrhythmic	C01B			
Cardiac stimulants excluding cardiac glycoside	C01C		Often inadequate	Often inadequate

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	ATC code	STOPPFrail 2021[62a] Frail older adults with less than 1 year of life remaining	Morin 2018[123b] Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
			Initiation	Continuation
Nitroglycerin	C01DA02			
Antihypertensives	C02	PIM	Often inadequate	
Antihypertensive, excluding alpha-blockers	C02			Often inadequate
Clonidine	C02AC01			
Alpha-blocker antihypertensives	C02CA, C02LE			Questionable
Hydralazine	C02DB02			
Diuretics	C03			
Low-ceiling diuretics, thiazides	C03A		Questionable	Questionable
Low-ceiling diuretics, non-thiazides	C03B		Questionable	Questionable
High-ceiling diuretics, excluding furosemide and torasemide	C03C		Questionable	
Other high-ceiling diuretics	C03C			No consensus
Furosemide	C03CA01		No consensus	No consensus
Torasemide	C03CA04		No consensus	No consensus
Potassium-sparing agents	C03D		Questionable	
Potassium-sparing agents, excluding spironolactone	C03D			Questionable
Spironolactone	C03DA01			No consensus
Peripheral vasodilators	C04		Often inadequate	Often inadequate
Beta-blocking agents	C07		Questionable	
Non-selective beta-blockers	C07AA			Questionable
Selective beta-blockers	C07AB			No consensus
Alpha- and beta-blocking agents	C07AG			No consensus
Calcium channel blockers	C08			Questionable
Calcium channel blockers, excluding verapamil	C08		Questionable	
Nimodipine	C08CA06			
Verapamil	C08DA01		Often inadequate	
Angiotensin-converting-enzyme inhibitors	C09A, C09B		Often inadequate	Questionable
Angiotensin II antagonists (sartans)	C09C, C09D		Often inadequate	Questionable
Lipid-modifying agents	C10		Often inadequate	Often inadequate
Statins	C10AA	PIM		

TABLE 5 (Continued)

Medication/medication class	ATC code	STOPPFrail 2021[62a]	Morin 2018[123b]	
			Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
Definition of frailty with limited life expectancy		Frail older adults with less than 1 year of life remaining	Initiation	Continuation
Ezetimibe	C10AX09	PIM		
Bile acid sequestrants	C10AC	PIM		
Fibrates	C10AB	PIM		
Nicotinic acid	C10AD02	PIM		
Acipimox	C10AD06	PIM		
Lomitapide	C10AX12	PIM		
Dermatologicals				
Antifungal creams	D01			
Genitourinary system and sex hormones				
Sex hormones	G03			
Systemic oestrogens for menopausal symptoms	G03C	PIM		
Raloxifene	G03XC01			
Urinary muscarinic antagonists/urologic spasmolytic/bladder relaxant/drugs for urinary incontinence	G04BD	PIM	Often inadequate (except oxybutynin)	No consensus
Oxybutynin	G04BD04		Questionable	No consensus
Mirabegron	G04BD12	PIM		
Drugs for prostatic hypertrophy, excluding finasteride	G04C		Questionable	No consensus
Finasteride	G04CB01, G04CA51		Often inadequate	Questionable
Alpha-adrenergic blockers	G04CA	PIM		
Tamsulosin	G04CA02			
5-Alpha reductase inhibitors in catheterised male patients	G04CB	PIM		
Systemic hormonal preparations, excluding sex hormones and insulins				
Systemic corticosteroids	H02	PIM (long term use)		
Mineralocorticoids	H02AA		No consensus	No consensus
Glucocorticoids for systemic use	H02AB		Often adequate	Often adequate
Thyroid hormones	H03AA		No consensus	Often adequate
Anti-thyroid drugs	H03B		Questionable	No consensus
Iodine therapy	H03C		Questionable	Questionable

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	ATC code	STOPPFrail 2021[62a] Frail older adults with less than 1 year of life remaining	Morin 2018[123b] Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
			Initiation	Continuation
Teriparatide	H05AA02	PIM		
Calcitonin	H05BA			
Anti-infective for systemic use				
Antibacterial	J01			
Antivirals	J05			
Antineoplastic and immunomodulating agents				
Antineoplastic drugs	L01		Often inadequate	Questionable
Endocrine therapies	L02		Often inadequate	Questionable
Hormone antagonists	L02B			
Antiestrogens	L02BA			
Antiandrogens	L02BB			
Immunostimulant	L03A		Often inadequate	Often inadequate
Immunosuppressant	L04A		Often inadequate	Questionable
Musculo-skeletal system				
Long-term oral NSAIDs	M01A	PIM		
Acetic acid derivatives	M01AB		No consensus	No consensus
Propionic acid derivatives	M01AE		No consensus	No consensus
Coxibs	M01AH		No consensus	No consensus
Capsaicin	M02AB01			
Muscle relaxant	M03		No consensus	No consensus
Baclofen	M03BX01		No consensus	No consensus
Anti-gout medications, excluding colchicine	M04		Questionable	
Anti-gout drugs, excluding allopurinol and colchicine	M04			Questionable
Allopurinol	M04AA01			No consensus
Colchicine	M04AC01		No consensus	No consensus
Bisphosphonates	M05BA	PIM	Often inadequate	Often inadequate
Other osteoporosis drugs	M05B		Often inadequate	Often inadequate
Strontium	M05BX03	PIM		
Denosumab	M05BX04	PIM		
Pressure ulcer products				

(Continues)

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	ATC code	STOPPFrail 2021[62a] Frail older adults with less than 1 year of life remaining	Morin 2018[123b] Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
			Initiation	Continuation
Nervous system				
Anaesthesia				
Ketamine	N01AX03		No consensus	No consensus
Nitrous oxide	N01AX13		No consensus	No consensus
Lidoderm	N01BB20			
Analgesics				
Opioid analgesics	N02A		Often adequate	Often adequate
Non-opioid analgesics	N02B		Often adequate	Often adequate
Antiepileptic's	N03		Often adequate Excluding drugs (eg, gabapentin, pregabalin, amitriptyline) prescribed for the management of neuropathic pain	Often adequate Excluding drugs (eg, gabapentin, pregabalin, amitriptyline) prescribed for the management of neuropathic pain
Clonazepam	N03AE01		Often adequate	
Gabapentin for neuropathic pain	N03AX12		No consensus	No consensus
Levetiracetam	N03AX14		Often adequate	
Pregabalin for neuropathic pain	N03AX16		No consensus	No consensus
Anti-Parkinson drugs				
Levodopa	N04BA		No consensus	Often adequate
Dopamine agonists	N04BC			No consensus
Other anti-Parkinson drugs	N04			No consensus
Psycholeptics				
Antipsychotics	N05A	PIM	No consensus	No consensus
Phenothiazine	N05AA, N05AB, N05AC			
Levomepromazine	N05AA02		No consensus	No consensus
Haloperidol	N05AD01		No consensus	No consensus
Olanzapine	N05AH03		No consensus	No consensus
Quetiapine	N05AH04			
Risperidone	N05AX08			
Anxiolytics	N05B			
Benzodiazepines: anxiolytics	N05BA		Often adequate	Often adequate
Other anxiolytics	N05B		No consensus	No consensus

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	ATC code	STOPPFrail 2021[62a] Frail older adults with less than 1 year of life remaining	Morin 2018[123b] Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
			Initiation	Continuation
Diazepam	N05BA01			
Oxazepam	N05BA04			
Hydroxyzine	N05BB01			
Hypnotics and sedatives	N05C			
Hypnotics and sedatives, excluding benzodiazepines	N05C		Questionable	No consensus
Benzodiazepines: hypnotics and sedatives	N05CD		No consensus	Often adequate
Benzodiazepines Z drugs	N05CF			
Zopiclone	N05CF01		No consensus	No consensus
Zolpidem	N05CF02		No consensus	No consensus
Zaleplone	N05CF03			
Eszopiclone	N05CF04		No consensus	No consensus
Nitrazepam	N05CD02			
Flunitrazepam	N05CD03			
Melatonin	N05CH01		No consensus	No consensus
Clomethiazole	N05CM02			
Psychoanaleptics				
Antidepressants	N06A			
Tricyclic antidepressants	N06AA		Questionable Excluding drugs (eg, gabapentin, pregabalin, amitriptyline) prescribed for the management of neuropathic pain	
Tricyclic antidepressants for neuropathic pain	N06AA		No consensus	No consensus
Tricyclic antidepressants for depression	N06AA			No consensus
Amitriptyline	N06AA09			
Doxepine	N06AA12			
Clomipramine	N06AA04			
Trimipramine	N06AA06			
Nortryptiline	N06AA10			
Selective serotonin reuptake inhibitors	N06AB		No consensus	No consensus
Monoamine oxidase inhibitors	N06AF, N06AG		Questionable	No consensus

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	ATC code	STOPPFrail 2021[62a] Frail older adults with less than 1 year of life remaining	Morin 2018[123b] Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
			Initiation	Continuation
Trazodone	N06AX05		No consensus	No consensus
Mirtazapine	N06AX11		No consensus	No consensus
Venlafaxine for neuropathic pain	N06AX16		No consensus	No consensus
Duloxetine for neuropathic pain	N06AX21		No consensus	No consensus
Central nervous system stimulants	N06B			
Citicoline	N06BX06			
Antidementia drugs	N06D		Often inadequate	Often inadequate
Memantine	N06DX01	PIM		
Other nervous system drugs				
Anticholinesterase inhibitors	N07AA			
Methadone	N07BC02		No consensus	No consensus
Antiparasitic products, insecticides and repellents				
Antiparasitic agents	P			
Respiratory system				
Decongestants	R01A,R01B			
Inhaled bronchodilators	R03A			
Salbutamol, inhalant	R03AC02		No consensus	Often adequate
Inhaled corticosteroids	R03BA		No consensus	Often adequate
Ipratropium, inhalant	R03BB01		No consensus	Often adequate
Other inhalants for COPD	R03B		No consensus	No consensus
Systemic drugs for obstructive airway diseases	R03C, R03D		Questionable	Questionable
Theophylline	R03DA04	PIM		
Aminophylline	R03DA05	PIM		
Leukotriene antagonists	R03DC	PIM		
Zafirlukast	R03DC01	PIM		
Montelukast	R03DC03	PIM		
Expectorants	R05CA			
Mucolytics	R05CB			
Antihistamine	R06			
Dexchlorpheniramine	R06AB02			

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	ATC code	STOPPFrail 2021[62a] Frail older adults with less than 1 year of life remaining	Morin 2018[123b] Estimated life expectancy of ≤3 months (75 years or older): initiation and discontinuation	
			Initiation	Continuation
Trimeprazine (limemazine)	R06AD01			
Promethazine	R06AD02			
Cyclizine	R06AE03		No consensus	No consensus
Meclizine: antivertigo agents	R06AE05			
Sensory organs				
Antiglaucoma drops	S01E			
Antiinflammatory eye drops	S01B			
Lubricating eye				
Drops				
Any preventive medicine				
General criteria				
Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations		PIM		
Any drug without clear clinical indication		PIM		
Any drug for symptoms which have now resolved (eg, pain, nausea, vertigo, pruritus)		PIM		

Abbreviations: ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical; Coxibs, cyclooxygenase-2-selective inhibitors; PIM, potentially inappropriate medications; PPI, proton pump inhibitor; SNRI, selective norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

[a]STOPPFrail 2021 criteria applied for patients with end-stage irreversible pathology, poor 1-year survival prognosis, severe functional impairment or severe cognitive impairment or both, and symptom control is the priority rather than prevention of disease progression.

[b]The Morin 2018 criteria provide a comprehensive classification for medication appropriateness at the end of life, encompassing both new medication initiation and continuation for patients already on treatment. "Often adequate" drug prescribing involves medications that are appropriate and beneficial for symptom management and comfort during the end-of-life period, essential for improving the patient's quality of life and addressing palliative care needs. "Questionable" drug prescribing includes medications for which appropriateness is uncertain, necessitating careful evaluation of potential benefits and risks based on the patient's condition and goals of care. "Often inadequate" drug prescribing refers to medications unsuitable for end-of-life care, often used for long-term chronic disease prevention or treatment, not aligned with the main focus of palliative care. "Not consensus" is applied when there is limited agreement among experts regarding medication appropriateness (if level of agreement was <75%).

[c]Holmes 2008: Categorized medications for use in advanced dementia into five groups based on the consensus of 12 experts. The classification aimed to guide appropriate medication management in palliative care for patients with advanced dementia. The categories include medications that are "Never appropriate", having no use in palliative care and should be stopped or not started; "Rarely appropriate", seldom used in palliative care and likely to be discontinued; "Sometimes appropriate", with uses depending on palliative care indications and potential continuation despite risks; "Always appropriate", useful in palliative care and suitable for continuation or initiation without reservations; and "No consensus (<7/12) agreement", indicating uncertainty among experts, requiring further evaluation and discussion.

[d]Eligible to deprescribe: Medications eligible for deprescribing are those with limited benefits that are suitable targets for discontinuation, and their need for continued use should be reassessed.

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Alimentary tract and metabolism					
Drugs for acid-related disorders, excluding PPIs					
H2 receptor antagonist	Sometimes appropriate	PIM			
Proton pump inhibitors	Sometimes appropriate	PIM		PIM	
Antispasmodics	Rarely appropriate				
Butylscopolamine					
Metoclopramide					
Antiemetics and antinauseants	Always appropriate				
Drugs for constipation/ laxatives	Always appropriate				
Antidiarrheal	Always appropriate				
Antidiabetic drugs					
Insulin	Sometimes appropriate				
Fast-acting insulin					
Intermediate-acting insulin					
Combined insulin					
Long-acting insulin					
Oral diabetic agents	Sometimes appropriate	PIM			
Other oral antidiabetics, excluding metformin			Eligible to deprescribe		
Metformin		PIM	Eligible to deprescribe		
Sulfonylureas		PIM		PIM	
Acarbose		PIM			
Thiazolidinediones		PIM			
Dipeptidyl peptidase 4 inhibitors		PIM			
Glucagon-Like Peptide-1 analogues		PIM			
Vitamins	No consensus	PIM			

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Multivitamin combination supplements					
Vitamin D			Eligible to deprescribe		
Minerals	No consensus	PIM			
Calcium supplement			Eligible to deprescribe		
Nutritional supplements (other than vitamins)	Sometimes appropriate				
Complementary-alternative medicines		PIM			
Appetite stimulants	Rarely appropriate				
Blood and blood-forming organs					
Vitamin K antagonists					
Warfarin	Rarely appropriate				
Unfractionated heparin	Rarely appropriate				
Low molecular weight heparin	Rarely appropriate				
Platelet aggregation inhibitors					
Antiplatelet agents, excluding aspirin	Never appropriate				
Aspirin	No consensus	PIM	Eligible to deprescribe		
Oral anticoagulants			Eligible to deprescribe		
Novel oral anticoagulants					
Other anticoagulants					
Antianaemic preparations					
Iron	No consensus				
Oral elemental iron doses >200 mg/day				PIM	
Iron preparations and erythropoietin					
Vitamin B12 and folic acid					
Folic acid					

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Red blood cell colony stimulating factors	No consensus				
Blood products					
Electrolytes	Sometimes appropriate				
Cardiovascular system					
Digitalis glycosides					
Digoxin	Rarely appropriate			PIM (>0.125 mg/day)	
Cardiac glycosides, excluding digoxin					
Antiarrhythmic	Rarely appropriate				
Cardiac stimulants excluding cardiac glycoside					
Nitroglycerin	Sometimes appropriate				
Antihypertensives		PIM	Eligible to deprescribe		Eligible to deprescribe
Antihypertensive, excluding alpha-blockers					
Clonidine	Rarely appropriate				
Alpha-blocker antihypertensives	Rarely appropriate				
Hydralazine	Rarely appropriate				
Diuretics	Sometimes appropriate				
Low-ceiling diuretics, thiazides		PIM			
Low-ceiling diuretics, non-thiazides					
High-ceiling diuretics, excluding furosemide and torasemide					
Other high-ceiling diuretics					
Furosemide					
Torasemide					

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Potassium-sparing agents					
Potassium-sparing agents, excluding spironolactone					
Spironolactone					
Peripheral vasodilators					
Beta-blocking agents	Sometimes appropriate	PIM			
Non-selective beta-blockers					
Selective beta-blockers					
Alpha- and beta-blocking agents					
Calcium channel blockers	Sometimes appropriate	PIM			
Calcium channel blockers, excluding verapamil					
Nimodipine			Eligible to deprescribe		
Verapamil					
Angiotensin-converting-enzyme inhibitors	Sometimes appropriate	PIM			
Angiotensin II antagonists (sartans)	Sometimes appropriate	PIM			
Lipid-modifying agents	Never appropriate				
Statins		PIM	Eligible to deprescribe		Eligible to deprescribe
Ezetimibe		PIM			
Bile acid sequestrants					
Fibrates		PIM			
Nicotinic acid					
Acipimox					
Lomitapide					
Dermatologicals					
Antifungal creams	Sometimes appropriate				
Genitourinary system and sex hormones					

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Sex hormones	Never appropriate				
Systemic oestrogens for menopausal symptoms					
Raloxifene		PIM			
Urinary muscarinic antagonists/urologic spasmolytic/bladder relaxant/drugs for urinary incontinence	Rarely appropriate		Eligible to deprescribe		Eligible to deprescribe
Oxybutynin					
Mirabegron					
Drugs for prostatic hypertrophy, excluding finasteride					
Finasteride	No consensus				
Alpha-adrenergic blockers	Rarely appropriate		Eligible to deprescribe		
Tamsulosin	Rarely appropriate				
5-Alpha reductase inhibitors in catheterised male patients					
Systemic hormonal preparations, excluding sex hormones and insulins					
Systemic corticosteroids	Sometimes appropriate			PIM (instead of inhaled corticosteroid)	
Mineralocorticoids	Rarely appropriate				
Glucocorticoids for systemic use					
Thyroid hormones	Sometimes appropriate				
Anti-thyroid drugs	Sometimes appropriate				
Iodine therapy					
Teriparatide					
Calcitonin	No consensus				
Anti-infective for systemic use					

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Antibacterial	Sometimes appropriate				
Antivirals	Sometimes appropriate				
Antineoplastic and immunomodulating agents					
Antineoplastic drugs	Never appropriate				
Endocrine therapies					
Hormone antagonists	Never appropriate				
Antiestrogens	Never appropriate				
Antiandrogens	Rarely appropriate				
Immunostimulant	Never appropriate				
Immunosuppressant	Never appropriate				
Musculo-skeletal system					
Long-term oral NSAIDs					PIM
Acetic acid derivatives					
Propionic acid derivatives					
Coxibs					
Capsaicin	Sometimes appropriate				
Muscle relaxant	No consensus				
Baclofen					
Anti-gout medications, excluding colchicine					
Anti-gout drugs, excluding allopurinol and colchicine					
Allopurinol	Sometimes appropriate		Eligible to deprescribe		
Colchicine	Sometimes appropriate				
Bisphosphonates	Rarely appropriate	PIM	Eligible to deprescribe		Eligible to deprescribe
Other osteoporosis drugs					
Strontium		PIM			
Denosumab		PIM			
Pressure ulcer products	Always appropriate				
Nervous system					

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Anaesthesia					
Ketamine					
Nitrous oxide					
Lidoderm	Always appropriate				
Analgesics					
Opioid analgesics	Always appropriate				
Non-opioid analgesics	Always appropriate				
Antiepileptic's	Always appropriate				
Clonazepam					
Gabapentin for neuropathic pain					
Levetiracetam					
Pregabalin for neuropathic pain					
Anti-Parkinson drugs					
Levodopa					
Dopamine agonists					
Other anti-Parkinson drugs					
Psycholeptics					
Antipsychotics	Sometimes appropriate			PIM (first generation)	Eligible to deprescribe
Phenothiazine				PIM	
Levomepromazine					
Haloperidol			Eligible to deprescribe		
Olanzapine					
Quetiapine			Eligible to deprescribe		
Risperidone			Eligible to deprescribe		
Anxiolytics	Always appropriate				
Benzodiazepines: anxiolytics			Eligible to deprescribe	PIM (>4 weeks)	
Other anxiolytics					

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Diazepam					PIM
Oxazepam					PIM (>30 mg/day)
Hydroxyzine					PIM
Hypnotics and sedatives	No consensus				PIM (regular use)
Hypnotics and sedatives, excluding benzodiazepines					
Benzodiazepines: hypnotics and sedatives			Eligible to deprescribe	PIM (>4 weeks)	
Benzodiazepines Z drugs			Eligible to deprescribe		
Zopiclone			Eligible to deprescribe		PIM (>5 mg/day)
Zolpidem			Eligible to deprescribe		
Zaleplone			Eligible to deprescribe		
Eszopiclone					
Nitrazepam					PIM
Flunitrazepam					PIM
Melatonin					
Clomethiazole					PIM
Psychoanaleptics					
Antidepressants	Sometimes appropriate		Eligible to deprescribe		Eligible to deprescribe
Tricyclic antidepressants	Sometimes appropriate			PIM	PIM
Tricyclic antidepressants for neuropathic pain					
Tricyclic antidepressants for depression					
Amitriptyline					PIM
Doxepine					PIM
Clomipramine					PIM
Trimipramine					PIM
Nortryptiline					PIM

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Selective serotonin reuptake inhibitors					
Monoamine oxidase inhibitors					
Trazodone					
Mirtazapine					
Venlafaxine for neuropathic pain					
Duloxetine for neuropathic pain					
Central nervous system stimulants	No consensus				
Citicoline			Eligible to deprescribe		
Antidementia drugs					
Memantine	Never appropriate				
Other nervous system drugs					
Anticholinesterase inhibitors	Never appropriate		Eligible to deprescribe		Eligible to deprescribe
Methadone					
Antiparasitic products, insecticides and repellents					
Antiparasitic agents	Sometimes appropriate				
Respiratory system					
Decongestants	Sometimes appropriate				
Inhaled bronchodilators	Always appropriate				
Salbutamol, inhalant					
Inhaled corticosteroids	Sometimes appropriate				
Ipratropium, inhalant					
Other inhalants for COPD					

TABLE 5 (Continued)

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Systemic drugs for obstructive airway diseases					
Theophylline					
Aminophylline					
Leukotriene antagonists	Never appropriate				
Zafirlukast					
Montelukast					
Expectorants	Always appropriate		Eligible to deprescribe		
Mucolytics	Sometimes appropriate		Eligible to deprescribe		
Antihistamine	Sometimes appropriate				PIM (first generation)
Dexchlorpheniramine					PIM
Trimeprazine (limemazine)					PIM
Promethazine					PIM
Cyclizine					
Meclizine: antivertigo agents	No consensus				
Sensory organs					
Antiglaucoma drops	Sometimes appropriate				
Antiinflammatory eye drops	Sometimes appropriate				
Lubricating eye	Always appropriate				
Drops	Always appropriate				
Any preventive medicine					Eligible to deprescribe
General criteria					
Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations					
Any drug without clear clinical indication					

TABLE 5 (Continued)

Medication/medication class Definition of frailty with limited life expectancy	Holmes 2008[101c] Palliative care patients with advanced dementia: functional assessment stage test score of 6E, 7A, 7B or 7C	OncPal deprescribing guidelines 2015[81] Palliative cancer patients: validated on patients <6 months of remaining life	List of evidence-baSed depreScribing for CHRONic patients[124d] Patients with multimorbidity	STOPP NH (US)[103] Residents in nursing home settings (the tool assumed that these populations have a limited lifespan)	NORGEP_NH[102] Residents in nursing home settings (the tool define this populations is frail)
Any drug for symptoms which have now resolved (eg, pain, nausea, vertigo, pruritus)					

Abbreviations: ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical; Coxibs, cyclooxygenase-2-selective inhibitors; PIM, potentially inappropriate medications; PPI, proton pump inhibitor; SNRI, selective norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

[a]STOPPFrail 2021 criteria applied for patients with end-stage irreversible pathology, poor 1-year survival prognosis, severe functional impairment or severe cognitive impairment or both, and symptom control is the priority rather than prevention of disease progression.

[b]The Morin 2018 criteria provide a comprehensive classification for medication appropriateness at the end of life, encompassing both new medication initiation and continuation for patients already on treatment. "Often adequate" drug prescribing involves medications that are appropriate and beneficial for symptom management and comfort during the end-of-life period, essential for improving the patient's quality of life and addressing palliative care needs. "Questionable" drug prescribing includes medications for which appropriateness is uncertain, necessitating careful evaluation of potential benefits and risks based on the patient's condition and goals of care. "Often inadequate" drug prescribing refers to medications unsuitable for end-of-life care, often used for long-term chronic disease prevention or treatment, not aligned with the main focus of palliative care. "Not consensus" is applied when there is limited agreement among experts regarding medication appropriateness (if level of agreement was <75%).

[c]Holmes 2008: Categorized medications for use in advanced dementia into five groups based on the consensus of 12 experts. The classification aimed to guide appropriate medication management in palliative care for patients with advanced dementia. The categories include medications that are "Never appropriate", having no use in palliative care and should be stopped or not started; "Rarely appropriate", seldom used in palliative care and likely to be discontinued; "Sometimes appropriate", with uses depending on palliative care indications and potential continuation despite risks; "Always appropriate", useful in palliative care and suitable for continuation or initiation without reservations; and "No consensus (<7/12) agreement", indicating uncertainty among experts, requiring further evaluation and discussion.

[d]Eligible to deprescribe: Medications eligible for deprescribing are those with limited benefits that are suitable targets for discontinuation, and their need for continued use should be reassessed.

components and remaining life expectancy. For paediatric patients, we found 152 PIPs and 29 PIOs. Notably, only two tools and eight guidelines following the GRADE framework provided information on the level of evidence for the medications/medication classes included. In older persons, we observed that only a quarter (24.7%, $n = 69/279$) of the medications were included in the list based on high-quality evidence.

To our knowledge, only one systematic review of systematic reviews reported 49 explicit tools to use for older adults.[14] In comparison with this review, we identified more explicit tools for a similar target population ($n = 72$) and looked at additional tools supporting the deprescribing process (ie, deprescribing guidelines). The higher numbers of tools identified in our review is justified by the fact that we included more years and used five databases, as opposed to the one database searched in the previous review.

During our review, we identified that for almost one-third of the tools, the settings where the tool could be applied were not specified. Additionally, we found that some tools had been adapted from existing non-specific settings to focus on a specific setting, such as nursing home residents, but made little to no changes in their list of medications, disregarding the differences in the characteristics of the target population, such as frailty aspects not being considered.[18,100] This lack of clear differentiation between the healthcare settings in which the tools should be implemented and the specific target groups for whom they are intended can potentially confuse users when they have to choose which tools to use for particular settings. In addition, although the majority of PIM lists have been validated using the Delphi consensus technique, there was variation in panel size, panel composition, the rating scale and the cut-off to determine whether the medication was a PIM or not. This variation could be a potential source of bias in consensus studies where the choice of rating scale had a substantial influence on the final consensus results.[9]

A (systematic) literature review of existing tools was the most common approach to tool development used by authors. Although the use of medications should be based on recommendations from well-established clinical trials, many drugs for children and older persons are used based on the experience of clinicians because, for ethical and practical reasons, generating evidence from clinical trials is difficult and evidence is mostly lacking for these populations.[67,154–156] The development of PIM lists based on high-quality evidence is therefore a challenging process, and this challenge might contribute to the prevalent trend of tools being developed based on existing PIM lists. In our study, 42.8% ($n = 36/84$) of explicit/mixed tools were developed based on existing tools. Fully relying on the content of existing tools for the development of new tools and adapting to other countries' drug availability (ie, including drugs as PIMs if the original tools classify the medication classes as PIMs) may introduce bias or lead to missing new medication or recent evidence.[35] To improve the quality and impact of the tool, combining the prior lists, considering clinical experience, and adding new evidence are required, and this can be achieved by regularly updating existing tools.

The initial aim of our review was to distinguish three groups of medications in different specific populations: appropriate medications, PIMs and medications for which a consensus has not been achieved. However, when scrutinizing the content of the existing tools, we had to slightly deviate from the protocol (CRD42021235348). For instance, medications classified as not PIMs are not always the same as those considered appropriate (eg, if a medication carries a known risk but the risk does not differ between younger and older adults, it was classified as not a PIM). Additionally, for tools developed for use in patients with limited life expectancy, the varied clinical components they addressed, along with the unspecified or varied duration of remaining life expectancy, added complexity. As a result of these complexities, we decided not to pool the medications from these tools into the prespecified three categories. Instead, we chose to classify them into broader categories. Consequently, we opted to provide a comprehensive overview of medications based on their various components. This approach facilitates the comparison of the appropriateness of medications for different clinical conditions and remaining life expectancy. Notably, medications primarily prescribed for symptom management, comfort or as beneficial for palliative care were generally classified as adequate or appropriate. In contrast, medications intended for the long-term prevention or treatment of chronic diseases tended to be labelled inappropriate or inadequate. Shrestha et al[157] also suggested categorizing medications into preventive, symptom-control and dual-purpose categories for patients with limited life expectancy. However, due to these complexities, developing the pooled list of medications based on existing tools without expert input and clearly defining limited life expectancy is challenging. Unclear definitions and the availability of tools for different time points in separate tools might be barriers for clinicians attempting to use the tools, therefore it is crucial to develop a unified list of PIMs for different time points of remaining life expectancy (eg, the last 3 months, 6 months, 1 year and 2 years) within a single tool.

Only a few tools reported the level of evidence used for their development. Even these tools and guidelines were mostly developed based on low- and moderate-quality evidence as opposed to high-quality evidence. This indicates that the currently available tools and guidelines were developed based on low-quality evidence and justifies the need to develop tools based on high-quality evidence. Developing tools based on high-quality evidence might not be achieved overnight, but regularly updating tools in line with new medication and newly generated evidence could improve the quality of evidence. For example, 21.1% of the Beers 2023 criteria were developed based on high-quality evidence,[58] whereas in Beers 2015 a lower number of criteria (18.5%) were developed based on high-quality evidence.[95] Notwithstanding, in our review, we only identified nine (9.5%) tools that have been updated at least once. Regularly updating the tools might not be a good solution in cases where evidence from individual-level studies is not continually generated. For instance, in patients with limited life expectancy, evidence is often lacking to formulate recommendations, therefore in addition to the development and updating of the tools based on expert consensus, the generation of evidence based on individual-level data is required to strengthen the level of evidence. The list of medications and the level of evidence included in our Excel files will help researchers in the selection of medications to generate

evidence and thus facilitate the strengthening of the level of evidence.

Overall, the low level of evidence and consensus methodology with different approaches might be reasons for the variations in the classification of medications across tools. For instance, rivaroxaban is considered to be a PIM in Beers 2023,[58] but is not classified as a PIM in PRISCUS 2023.[60] Heterogeneity in the list of medications between tools depending on the marketing and variation in the availability of drugs in the country developing the tool is to be expected, but assigning the same medications to different categories (PIM or not PIM) for similar target groups is difficult to explain. In fact, for some tools and guidelines, the varying levels of stringency applied during the validation process for the inclusion of medications in the list might be the reason for the discrepancy. This could consequently be a barrier to using tools in clinical practice or lead to the selection of different treatments depending on which tools are selected by clinicians. Clinical judgement therefore remains important when using the tools; they should be considered as an instrument to aid in the prescribing or deprescribing process without replacing the clinician's judgement. For future development of deprescribing tools and guidelines, a transparent approach that includes grading of evidence and sufficient information in their publications would greatly benefit clinicians and researchers. This approach would enhance the credibility and reliability of the tools, empowering healthcare professionals to make more informed decisions about medication appropriateness and deprescribing. Training clinicians about the pros and cons of using the tools is relevant, not to encourage indiscriminate use, but to equip them with the necessary skills and knowledge to critically evaluate evidence and make informed decisions.

Although this umbrella review provides a comprehensive and structured overview of existing tools and guidelines along with the level of evidence for the included medications, it also has some limitations. First, a limitation of the study is that, despite conducting an extensive search of research and guideline databases, there is a possibility that some tools that were published after the date of the initial search were missed, particularly new tools released in 2023 and tools that were not included in the systematic reviews. However, to address this limitation, we checked for updates and identified five tools that were updated in late 2022 and 2023 (until 7 July 2023).[56–60] Second, although the tools and guidelines were organized based on the target populations, we considered tools targeted for limited life expectancy as an umbrella term representing frailty, advanced diseases, end-of-life care situations and tools that do not provide frailty criteria but noted that these tools are intended for frail individuals (eg, nursing home residents). However, the estimated life expectancy for these components is not well defined in most of the literature and can vary. Third, we included the validated and most recent versions of the tools for medication extraction, using genealogy as a tool to describe a link between the tools. Thus, the medications of some earlier tools that are not linked with recent tools are extracted and included in the list, but some of these medications are rarely used or are no longer available on the market.

5 | CONCLUSION: IMPLICATIONS FOR CLINICAL PRACTICE AND FURTHER RESEARCH

Our structured overview of existing tools and guidelines, along with the level of evidence for the included medications, should enable clinicians and researchers to evaluate the strengths and weaknesses of different tools and guidelines for various purposes. This can help clinicians choose appropriate tools for specific settings/target populations and use them for shared decision-making. Our review offers extensive lists distinguishing PIMs, appropriate medications, drugs where consensus is not reached and therapeutic alternatives for PIMs for different target populations. This provides a wider overview of medication appropriateness for clinicians while prescribing medications and deprescribing PIMs for patients.

These compiled medication lists serve as a database (starting point) for researchers developing new medication appropriateness assessment tools, aid in medication selection for evidence generation and provide hypotheses to validate consensus-based classifications using real-world data. Overall, they will facilitate the efforts to be made in strengthening the level of evidence. However, compiling lists from tools targeting older adults with limited life expectancy proved challenging due to varying definitions of the target population across tools and guidelines. Thus, it is crucial to develop a list of appropriate, questionable medications and PIMs for different time points of remaining life expectancy in a single tool; this should involve international experts. In addition to the development of the tools based on a clear definition of limited life expectancy, individual-level data are required to strengthen the level of evidence, as this evidence is generally meagre or lacking.

The discrepancies in distinguishing the appropriateness of medications across tools could stem from the low level of evidence and variations in methodological development and validation. To address this, it is recommended that researchers developing the tool be transparent about their methodology, provide sufficient information for users and regularly update tools in line with new evidence. An international consensus on tool and guideline development might reduce the discrepancies between lists resulting from differences in rating scales and consensus criteria. This approach could also provide a broader context as well as the possibility of capturing the current available evidence and accounting for the prescribing behaviours of physicians in different countries. In future, the development and validation processes of medication lists should be clearer, more transparent and more adaptable to the intended settings, taking into account the unique characteristics of the target population.

AUTHOR CONTRIBUTIONS

Joachim Cohen, Tinne Dilles and Kristel Paque conceptualized and supervised the study. Degefaye Zelalem Anlay and Kristel Paque designed the study, extracted the data and conducted the analyses. Ellen Van Leeuwen reviewed the data extraction tools. Degefaye Zelalem Anlay drafted the initial versions of the manuscript. All authors provided feedback on the analysis and interpretation of the

data and critically revised the manuscript. All authors read and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data are included in the manuscript and the Supporting Information files.

ORCID

Degefaye Zelalem Anlay https://orcid.org/0000-0002-7566-9548

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SUPPORTING INFORMATION

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