Tools for Deprescribing in Frail Older Persons and Those with Limited Life Expectancy

A Systematic Review

Thompson, Wade; Lundby, Carina; Graabaek, Trine; Nielsen, Dorthe S; Ryg, Jesper; Søndergaard, Jens; Pottegård, Anton

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Tools for deprescribing in frail older persons and those with limited life expectancy: a systematic review

Running title: Deprescribing tools

Wade Thompson PharmD MSc1, Carina Lundby MScPhm2, Trine Graabæk MScPhm PhD2, Dorthe S Nielsen MD PhD3,4,5, Jesper Ryg MD PhD6,7, Jens Søndergaard MD PhD1, Anton Pottegård MScPhm PhD @APottegard2,8

(1) Research Unit of General Practice, Department of Public Health, University of Southern Denmark, Odense C, Denmark
(2) Hospital Pharmacy of Funen, Odense University Hospital, Odense C, Denmark
(3) Migrant Health Clinic, Odense University Hospital, Odense C, Denmark
(4) Centre for Global Health, University of Southern Denmark, Odense C, Denmark
(5) Health Sciences Research Center, University College Lillebaelt, Odense M, Denmark
(6) Department of Geriatric Medicine, Odense University Hospital, Odense C, Denmark
(7) Geriatric Research Unit, Department of Clinical Research, University of Southern Denmark, Odense C, Denmark
(8) Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense C, Denmark

*Corresponding author
wthomp01@gmail.com
+45 2077 9527
@wthomp01

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Impact statement: This review is novel. While previous reviews have summarized available deprescribing tools, none have focused specifically on frail older persons and those with limited life expectancy. When considering deprescribing in this population, it will be helpful for clinicians to be aware of, and use the most relevant and applicable tools. Our work adds to previous reviews in that we provide an up-to-date systematic search of deprescribing tools and focus on frail older persons and those with limited life expectancy. We also identify tools not highlighted by previous reviews.
Abstract

Background
Frail older persons and those with limited life expectancy are often prescribed medications that are potentially inappropriate. Harms may outweigh benefits, time to benefit may exceed life expectancy, and medications may not be consistent with goals of care.

Objective
To summarize available tools that can assist clinicians in identifying and reducing/stopping (deprescribing) such medications and which specifically consider frailty or limited life expectancy in their process.

Design
Systematic review and narrative synthesis.

Setting
We searched MEDLINE (via Ovid SP), EMBASE (via Ovid SP), and CINAHL from inception to December 2017 along with grey literature. We included articles that described a tool to guide deprescribing of medications.

Participants
Frail older persons and those with limited life expectancy.

Measurements
Narrative description of tools.

Results
We identified 15 tools and organized them into three main categories: (1) tools (n=2) that described a model or framework for approaching deprescribing, (2) tools (n=9) that outlined a deprescribing approach for the entire medication list, and (3) tools (n=4) that provided medication-specific advice. The complexity of the tools ranged from simple lists to detailed, step-wise protocols. The development methodology varied widely and the methods used to synthesize the tools were generally not well-described. Most tools were based on expert opinion. Only four out of the 15 tools have been tested in clinical practice (in very low-quality studies).

Conclusion
Tools exist to help clinicians deprescribe in frail older persons and those with limited life expectancy. These tools may assist clinicians at various stages in the deprescribing process. However, it remains to be investigated whether the use of such tools in practice is likely to improve clinical outcomes or reduce inappropriate medication use.
Introduction

Older persons often take many medications [1] and are more susceptible to the adverse effects of medications compared to younger persons [2,3]. Polypharmacy has been defined as concomitant use of multiple medications (often arbitrarily defined as use of ≥5 or ≥10 medications), use of medications that are not indicated, or use of medications where harms outweigh benefits [4,5]. Regardless of the definition, the prevalence of polypharmacy is increasing in older persons [6] and it is associated with an increased risk of adverse health outcomes such as increased risk of falls, adverse drug events, and hospitalizations, even when accounting for co-morbidities [4,7]. In frail older persons and those with limited life expectancy, there is also a lack of evidence of benefit for some common treatments [8], e.g. statins or intensive blood glucose control in type 2 diabetes. However, this population may continue on such treatments [9] without reassessment when the potential for harm may outweigh the potential for benefit. Older persons may also be started on medications where the known time to benefit exceeds life expectancy [10,11]. Finally, goals of drug treatment may also shift from reducing risk of disease and prolonging life to maintaining quality of life and reducing treatment burden [8].

When medications are potentially inappropriate due to the reasons outlined above, patients and prescribers may be interested in reducing or stopping them. Deprescribing is the planned, supervised dose reduction or stopping of a medication [12]. Deprescribing is often viewed as challenging by prescribers [13,14]; however, some resources are available to help clinicians with deprescribing decisions. These range
from focusing on screening for potentially inappropriate medications (e.g. Beers criteria and Screening Tool of Older People’s Prescriptions [STOPP] criteria), providing a general framework on the deprescribing process, and giving medication-specific guidance [15].

The range of tools available to support deprescribing has been summarized in 2012 [15] and 2017 (search conducted December 2015) [16]; however, neither of these reviews focuses on frail older persons or those with limited life expectancy specifically. While deprescribing is important to consider at all stages of medical care, it is particularly important in frail older patients and those with limited life expectancy for the reasons outlined above. Thus, it will be helpful for clinicians to be aware of, and use the deprescribing tools that are most applicable to this population.

With this systematic review, we aimed to identify and describe tools focused on deprescribing medications in frail older persons and those with limited life expectancy. We wanted to (1) provide an overview of tools which clinicians can use to manage polypharmacy in this population and (2) identify what is needed from future studies within the field.
Methods

We conducted a systematic review with narrative synthesis, following the PRISMA guidelines [17].

Population

The population of interest was frail older persons and those with limited life expectancy. Therefore, we were only interested in tools which were aimed at this population (or specifically included this population in their approach). We excluded tools that were aimed exclusively at patients with cancer in the palliative care setting.

Tools

Tools could be algorithms, guidelines, websites, scientific publications, or any other resource which provides guidance on deprescribing of medications in our population of interest (either for an overall medication list or medication-specific advice).

Search strategy

We searched the following databases from inception to December 2017: MEDLINE (via Ovid SP), EMBASE (via Ovid SP), and CINAHL. We used the following search strategy: (frail OR elderly OR old OR older OR “end of life” OR “eol” OR “life-limiting illness”) AND (deprescribe OR deprescribing OR deprescription OR "medication cessation" OR "medication withdrawal" OR "medication discontinuation" OR “inappropriate prescribing” OR “inappropriate medications” OR “inappropriate medication” OR “unnecessary...
prescription” OR “unnecessary prescriptions”). The search strategy was broad as the search was also used to capture articles for two other reviews on deprescribing. We also searched the bibliographies of eligible studies and known major works in the field of deprescribing to identify tools. Finally, we conducted a grey literature search using Google, Google Scholar, UpToDate, the TRIP database, clinicaltrials.gov, and the WHO register for clinical trials. We only included articles in English.

Screening

Two authors (CL, TG) screened titles and abstracts retrieved from databases and grey literature against the eligibility criteria described above. If articles or resources were possibly relevant, the full text was retrieved. Two authors (CL, WT) then screened the full text articles and grey literature for eligible publications or resources. Covidence was used as a screening tool [18]. Disagreements were resolved by all authors. The final study selection was discussed by the full author group and all authors agreed on the final decision for inclusion of articles.

Data extraction and synthesis

One author (WT) went through eligible articles and resources and extracted the following information: tool name, publication year, who developed the tool, development methodology, and whether the tool has been tested or evaluated. We summarized the extracted information narratively to provide a brief, structured overview of the tools that exist.
Results

Our search produced 2,149 titles and abstracts after removing duplicates. We reviewed 144 full-text articles and resources out of which 15 tools were eligible for inclusion (Figure 1). A total of four studies addressed patients with limited life expectancy, four studies addressed frail older persons, whereas seven studies assessed both categories. The characteristics of the tools are briefly summarized in Table 1 and further detail is available in the Supplementary Material.

We identified three main categories of tools based on our search results. Two tools described a model or framework for approaching deprescribing [19,20], nine tools outlined a deprescribing approach for the patient’s entire medication list [21–29], and four tools provided guidance on deprescribing of individual medications [30–33]. A summary of the features of each of these three categories is outlined in Figure 2.

Three of the tools were developed using Delphi methodology [24,26,29], two were developed using a systematic review and GRADEing of evidence (explicit and systematic method for rating quality of evidence and synthesizing recommendations) [30,31], one tool was developed from a literature review [27], one from an expert panel reviewing literature [32], and eight tools did not describe the development methodology [19–23,25,28,33]. Six of the tools were developed by a formally organized panel of experts [24,26,29–32] while eight of the tools were developed by study authors (experts in the field) [19–23,27,28,33]. The person(s) responsible for developing one of the tools
was not described [25]. Four of the tools have been implemented and evaluated in prospective studies (see Supplementary Material for further details) [20,21,25,28]. A reliability study has been conducted for one of the tools [34].

Tools employed different approaches for identifying frailty or limited life expectancy. Specific scales or indices used included: life tables [19], NECPAL-CCOMS-ICO [20], Clinical Frailty Scale [21,31,32], Mortality Score [21], PROFUND index [29], Pfeiffer questionnaire [29], Barthel Index [29], and the Functional Assessment Stages (FAST) score [35]. The STOPPFrail tool used the following criteria: end-stage irreversible pathology, age ≥65 years, poor one-year survival prognosis, severe functional and/or cognitive impairment, and goal of symptom control versus prevention of disease progression [24]. Garfinkel et al. did not use specific criteria but this tool was designed for use in nursing home patients [28]. Similarly, the algorithm from Frank et al. did not provide specific criteria for frailty or limited life expectancy but noted that their tool was intended for those who are frail [27]. Pruskowski et al. applied their tool to persons residing in a nursing home with a comfort-focused treatment plan [25]. The tools developed by Scott et al. did not endorse specific criteria but a core component of the tool was assessing life expectancy and functional limitations [22,23]. The tools from Primary Health Tasmania did not describe measures to assess life expectancy or frailty [33]. Reeve et al. did not recommend specific criteria for limited life expectancy but suggested that their tool could be applied to patients with advanced dementia characterized by dependence in most activities of daily living and inability to respond to their environment [30]. Finally, Farrell et al. did not endorse a specific measure for life
expectancy or frailty but discussed the use of the Clinical Frailty Scale, as well as hypoglycemia unawareness, co-morbidities, and functional limitations [31].
Discussion

A variety of tools exist to assist clinicians with deprescribing in frail older persons or those with limited life expectancy. While a number of deprescribing tools currently exist, we have identified those which specifically address deprescribing in frail older persons and those with limited life expectancy. This will allow clinicians to use the most applicable tools when considering deprescribing in this population. As outlined in Figure 2, we could categorize tools based on where they would be used during the deprescribing process. We saw the deprescribing process as a continuum where a clinician would first need high-level instruction of how to approach deprescribing (i.e. a deprescribing mindset), second to evaluate the entire medication list, and lastly require guidance on how to deprescribe one or more specific medications.

Models or frameworks
The first category of tools highlights a high-level model or framework for making medication decisions in older persons with limited life expectancy. These tools outline a way of thinking about or approaching medication use in the population of interest. For example, the model proposed by Holmes et al. [19] offers that medication use in those with limited life expectancy should consider the time to benefit of a medication, life expectancy, goals of care, and whether a medication is likely to achieve goals or targets. Similarly, Molist Brunet et al. [20] outline a multiple-step patient-centered approach for making medication decisions in older persons with limited life expectancy, including a comprehensive assessment of the patient’s clinical status, diagnosis-specific
status, and medications incorporated with goals of care and shared-decision making at every step.

Clinicians may require guidance on estimating life expectancy to aid medication decisions. Various methods have been proposed though many are unvalidated and with unknown accuracy [36]. As such, these measures can be considered mainly as rough guides that may be helpful to inform approximate estimation of life expectancy. A detailed discussion of this topic is beyond the scope of this review, though we will highlight some methods which have been proposed. Holmes et al. suggest that life tables can be used for insight on life expectancy (which account for persons who may be more or less healthy than average, based on the presence of multiple co-morbidities and/or functional impairment, for example) [19,37]. Molist Brunet et al. categorized patients as having limited life expectancy based on the NECPAL CCOMS-ICO tool [20]. Mortality indices and online calculators have also been suggested as ways to estimate life expectancy in the context of medication decisions [37,38]. Finally, the “surprise question” (would you be surprised if this patient died in the next 12 months?) is a method which has been used to predict mortality in patients with advanced illness, though its performance is poor in noncancer illness [39,40].

**Approaching the entire medication list**

The second category features tools which describe approaches to identify and prioritize drugs for deprescribing. These tools give advice on general principles to use when evaluating the whole medication list. For example, weighing the benefits and harms of
the medications, considering whether a medication is likely to help a patient achieve goals of care, and considering burden of treatment. The tools in this level differ considerably in terms of comprehensiveness. Some of the tools provide a stepwise approach or algorithm to evaluating a patient's medication list. These tools provide general instructions or considerations at each step, with some examples [21–23,27,28]. Other tools in this category provide a list of medications, with deprescribing considerations or criteria for each medication/medication class [24,29]. For example, providing a drug class and identify conditions under which deprescribing may be considered [29]. Some of the tools also contain considerations for monitoring and follow-up, although they do not provide great detail [22,23,29]. For example, Scott et al. discuss general principles such as educating patients on what to monitor for and to wean patients off drugs likely to cause adverse withdrawal effects [23]. Rodriguez-Perez et al. also offer brief suggestions regarding follow-up after deprescribing for specific medication classes [29]. Finally, some tools in this category are simply a list of medications, which could be considered for deprescribing with no specific details or considerations [25,35]. Tools which contain lists of medications may be useful in screening for potential candidates for deprescribing from an entire medication list. Once a potential medication is identified, a clinician could use the more detailed approaches from the step-wise tools or algorithms. While more detailed tools [22,23,29] provide useful advice for deprescribing, it may still be challenging to deprescribe individual medications in practice. Clinicians may want detailed information on tapering, monitoring, or weighing benefits/harms for specific drugs. Thus, clinicians could also consult tools that provide detailed guidance on deprescribing of individual medications.
Medication-specific tools

While the tools from the second category are useful in identifying which drugs can be deprescribed, the tools in this category go into more detail on how to approach deprescribing for individual drugs. Some of the tools in the second category do provide considerations for developing deprescribing plans; however, the advice provided in those tools is general. The tools in the third category therefore build on the second category in giving detailed monitoring and tapering advice as well as considerations on benefits and harms for specific medications. Tools in the third category also differ in terms of comprehensiveness and scope. Some of the tools focus primarily on weighing the benefits and harms of an individual medication (i.e. how to decide whether to continue or deprescribe that individual medication) [32]. For example, the Palliative and Therapeutic Harmonization (PATH) clinic guidelines primarily outline and analyze the clinical evidence (or lack thereof) and considerations for using various preventive medications in frail older persons [41–43]. Other tools provide guidance on both how to approach deprescribing decisions and how to deprescribe the medication [30,31]. For example, the tools and guidelines from Farrell et al. and Reeve et al. [30,31] outline specific details about frequency of monitoring and tapering rate for specific medications and medication classes. They also include detailed considerations for assessing whether an individual medication can be deprescribed (e.g. weighing benefits and harms of continued use, considering patient values and preferences surrounding a specific medication or class). Thus, they may be particularly helpful in providing targeted guidance for a specific medication or class.
Development methods for the tools

Eight of the tools we identified provided no description of development and appeared to be based on expert opinion of the authors. One study described a non-systematic literature review to inform tool development; however, the authors did not conduct a systematic search and the approach for synthesizing the tool from the literature was not described [27]. Another group described use of an expert committee to develop recommendations based on available literature, though the methods for synthesizing recommendations was not provided [32]. While some of the steps, considerations, and recommendations provided in these tools may be informed by evidence, this is not explicitly described. Therefore, it is difficult to gauge which areas are informed by evidence and which by expert opinion or clinical judgement. Although there is generally limited evidence on pharmacotherapy in frail older persons [8,44], it would be helpful to understand how steps or recommendations were arrived at (especially considering expert opinion is acknowledged as the lowest level on the evidence-based medicine pyramid) [45].

Three of the tools were developed using Delphi methodology [24,26,29]. In these tools, the methodology for arriving at recommendations is explicit and well described. However, the recommendations in such tools were also based on expert opinion given the methodology used. While some of the recommendations may be informed by evidence, it is difficult to evaluate the extent to which the criteria are evidence-based.
Finally, two tools were based on evidence from systematic reviews and an explicit approach for developing recommendations from evidence [30,31]. While these tools were developed using more rigorous methods, given scant evidence on the topics some of the content of the tools was also based primarily on expert opinion.

The fact that much of the content of the tools is based on expert opinion is not surprising given the paucity of evidence in this field. However, the tools also varied considerably in how well the development methodology was described. This ranged from an explicit and well-described approach to how recommendations, steps, or considerations were arrived at, to no description of development methodology.

*Implementation of tools*

Four of the fifteen studies identified have been tested in prospective studies [20,21,25,28]. Three of the studies used an uncontrolled before-after design [20,21,25]. They measured the number of changes made to medication regimens and the rate of discontinuation of medications after the intervention. One study tested their tool using a controlled before-after study [28]. This study measured the discontinuation rate in the intervention group and compared mortality and acute care referrals in the intervention group and control group. This study was not randomized and the developer was the only clinician implementing the tool. While these studies would be considered very low-quality evidence due to their non-randomized design and small sample sizes [46], they do suggest that these tools may be useful in reducing the number of medications.
patients are taking. However, they provide little insight on the potential clinical effects of using the deprescribing tools.

Eleven of the tools developed have not been tested in clinical practice. Therefore, it is unclear whether using these tools is likely to result in a meaningful reduction in inappropriate medication use and improve outcomes or even cause harm [47]. A previous review has also noted this limitation [16]. Lack of clinical outcome data and inconsistency in outcome measurement have also been highlighted as limitations in deprescribing studies to date [48,49]. A 2018 systematic review evaluating deprescribing interventions in older persons found that few studies measured clinical outcomes and none were adequately powered to detect differences in clinical outcomes between intervention and control groups [50]. A number of deprescribing tools have been developed in recent years; however, these remain largely untested [16]. Instead of simply developing more and more tools, researchers and clinicians should focus on developing quality tools using systematic and explicit methods. Ideally, such tools should be tested in well-designed clinical trials that are adequately powered to measure meaningful clinical outcomes. Trials should clearly describe their implementation approach to allow for reproducibility of the intervention.

**Strengths and limitations**

We used a systematic search to identify tools, with screening performed by two authors and all authors approving final study selection. By focusing our review on those which are applicable to frail older persons and those with limited life expectancy, we provide
insight into the tools most applicable to this population. Our search was limited by excluding the language to only English. We were also unable to access four full-text articles.

Conclusion

We identified 15 tools which could be used during the deprescribing process in frail older persons and those with limited life expectancy. Individual tools are likely useful to clinicians at different stages of deprescribing. Tools could be used: (1) as a model or framework for pharmacotherapy in persons with limited life expectancy (i.e. a way of thinking), (2) to approach the entire medication list (i.e. a global approach), and (3) to guide deprescribing of a specific medication or medication class (i.e. medication-specific guidance). Much of the content of the tools was based on expert opinion or clinical experience. Development methodology was poorly described for the majority of tools. Finally, only four out of 15 tools have been tested in clinical practice (and these were considered very low-quality studies). It is largely unclear whether existing tools are likely to improve the quality of prescribing and improve clinical outcomes or even cause harm. Future work should focus on developing tools according to explicit and rigorous methods and testing developed tools in well-designed clinical trials that measure clinically important outcomes.
Acknowledgements

Conflict of interest
The authors have no conflicts of interest to declare.

Contributions
AP, JR, JS, and DSN conceived the study. All authors designed the study. TG, CL and WT completed the screening process with input from AP, JR, JS and DSN. WT extracted data and all authors provided input on synthesis/analysis. WT drafted the manuscript. All authors provided critical feedback and revisions on the manuscript. All authors approved the final version for submission.

Sponsor’s role
The sponsor had no role in the design of the study, collection of data, analysis of data, preparation of the manuscript or final approval of the manuscript.
References


21. McKean M, Pillans P, Scott IA. A medication review and deprescribing method for hospitalised older patients receiving


<table>
<thead>
<tr>
<th>Tool</th>
<th>Population of interest</th>
<th>Brief description</th>
</tr>
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<tbody>
<tr>
<td>Holmes 2006 [19]</td>
<td>Patients with limited life expectancy (based on life tables)</td>
<td>Model to guide discontinuing medications in patients with limited life expectancy</td>
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<tr>
<td>Molist Brunet 2015 [20]</td>
<td>Patients with limited life expectancy (based on NECPAL CCOMS-ICO)</td>
<td>Model for assessing pharmacotherapy, including considerations for discontinuing medications</td>
</tr>
<tr>
<td><strong>Entire medication list</strong></td>
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<td>Geriatric-Palliative algorithm [28]</td>
<td>Frail older persons (patients in nursing home with incurable disease)</td>
<td>Algorithm aimed at identifying whether a drug can be deprescribed based on indication, safety, alternative therapies</td>
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<td>Frail older persons (e.g. end-stage irreversible pathology, poor one-year survival prognosis, severe functional impairment, goal of symptom control)</td>
<td>List of criteria for specific medications and health conditions where deprescribing can be considered; provides suggested monitoring parameters</td>
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<tr>
<td>LESS-CHRON [29]</td>
<td>Older persons with multiple co-morbidities, specifically discuss frail older persons (criteria are medication-specific)</td>
<td>List of medications and conditions where deprescribing can be considered; provides monitoring and follow-up guidance</td>
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<td>Holmes 2008 [26]</td>
<td>Patients with advanced dementia (FAST score 6E, 7A, 7B, 7C)</td>
<td>List of medications to guide deprescribing; medications considered never appropriate, rarely appropriate, sometimes appropriate, always appropriate in advanced dementia</td>
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<td>McKean 2016 [21]</td>
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<td>Pruskowski 2017 [25]</td>
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<td>List of medications to consider deprescribing</td>
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<td>Frank 2014 [27]</td>
<td>Older persons, specific discussion of frail patients and those with limited life expectancy (no specific criteria described)</td>
<td>Algorithm to guide deprescribing process for entire medication list</td>
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<td>Scott 2015 [23]</td>
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<td><strong>Medication specific</strong></td>
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<tr>
<td>PATH Clinic guidelines [41–43]</td>
<td>Frail older persons (based on CFS)</td>
<td>Condition-specific guidelines (hypertension, CVD, diabetes) providing advice and guidance for when medications can be deprescribed</td>
</tr>
<tr>
<td>Deprescribing antihyperglycemic agents [31]</td>
<td>Older persons in general but discuss frail older persons and those with limited life expectancy (e.g. based on CFS)</td>
<td>Criteria and guidance for deprescribing diabetes medications</td>
</tr>
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<td>Deprescribing cholinesterase inhibitors and memantine [30]</td>
<td>Older persons in general but discuss those with limited life expectancy (advanced dementia- e.g. dependent on most ADLs)</td>
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<tr>
<td>A guide to deprescribing [33]</td>
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<td>Multiple medication-specific guides (e.g. statins, bisphosphonates) providing deprescribing rationale, instructions</td>
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**Abbreviations:** ADLs- activities of daily living; CFS- clinical frailty scale; CVD- cardiovascular disease; FAST-functional assessment stages; GRADE- Grading of Recommendations Assessment, Development and Evaluation; NECPAL CCOMS- Palliative Needs Tool; PATH- Palliative and Therapeutic Harmonization Program; STOPP-Screening Tool for Older People’s Prescriptions