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Novel tool for deprescribing in chronic patients with multimorbidity: List of Evidence-Based Deprescribing for Chronic Patients criteria

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Aim: To create a tool to identify drugs and clinical situations that offers an opportunity of deprescribing in patients with multimorbidity.

Methods: A literature review completed with electronic brainstorming, and subsequently, a panel of experts using the Delphi methodology were applied. The experts assessed the criteria identified in the literature and brainstorming as possible situations for deprescribing. They were also asked to assess the influence of life prognosis in each criterion. A tool was composed of the most appropriate criteria according to the strength of their evidence, usefulness in patients with multimorbidity and applicability in clinical practice.

Results: Out of a total of 100, 27 criteria were selected to be included in the final list. It was named the LESS-CHRON criteria (List of Evidence-baSed depreScribing for CHRONic patients), and was organized by the anatomical group of the Anatomical, Therapeutic, Chemical (ATC) classification system of the drug to be deprescribed. Each criterion contains: drug indication for which it is prescribed, clinical situation that offers an opportunity to deprescribe, clinical variable to be monitored and the minimum time to follow up the patient after deprescribing.

Conclusions: The "LESS-CHRON criteria" are the result of a comprehensive and standardized methodology to identify clinical situations for deprescribing drugs in chronic patients with multimorbidity. **Geriatr Gerontol Int 2017; ••: ••–••.**

Keywords: appropriateness, deprescribing, elderly, multimorbidity, polypharmacy.

Introduction

Patients with chronic diseases are an emerging population in most clinical areas.[1–3] Patients with multimorbidity (PMM) are an especially complex population among all chronic patients. The term, multimorbidity, is applied to those patients suffering from two or more complex, potentially disabling, chronic diseases and share common features, such as poor midterm outcomes, high percentages of disability and frailty, frequent hospital admissions, polypharmacy, and the risk of adverse drug reactions.[4,5]

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Patients with multimorbidity have a limited survival. The PROFUND index stratifies mortality risk in PMM populations based on nine predictive factors. It showed four risk categories with these probabilities of mortality in the derivation/validation cohorts: 12.1%/14.6% for patients with 0–2 points; 21.5%/31.5% for those with 3–6 points; 45%/50% for those with 7–10 points; and 68%/61.3% for those with ≥11 points, respectively.[4]

Polypharmacy is frequent among PMM,[3,6] and could result in a higher number of hospital admissions and higher frailty.[7] Patients with polypharmacy are also more vulnerable to drug-related problems.[8] Withdrawal of medications might be an appropriate clinical decision, and could result in significant clinical and functional benefits in PMM. Therefore, actions aimed at reducing polypharmacy must be a priority in PMM to decrease medication where the potential harms outweigh the

potential benefits, improving adherence and reducing costs.

Deprescribing is a review and evaluation process of long-term therapeutic plans aiming to stop, substitute or reduce the dosage of those drugs that under certain clinical conditions can be considered unnecessary or with an unfavorable benefit–risk ratio.[9,10] Its aim is to reduce the drug burden, reduce adverse drug reactions related to a high number of drugs on treatment and prevent prescribing cascades.

The approach to assess what drugs can be deprescribed is similar to the appropriateness approach: there are implicit and explicit methods. Regarding implicit methods, several processes that guide how to stop the drugs whose risk–benefit ratio is not favorable have been developed.[11,12] Recently, two revisions have described models based on five steps as suggested protocols to guide the deprescribing process within the doctor–patient encounter.[12,13] However, explicit methods seem not to be clearly defined yet. In the appropriateness approach, Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria and Beers criteria are widely accepted. However, in deprescribing, there are only some studies that used a predefined list of drugs as potential deprescribing targets,[14,15] and a specific tool has been developed only for oncological patients.[16] Therefore, developing a list of specific criteria as an explicit tool to reduce polypharmacy in PMM should be interesting.

The aim of the present study was to identify and select a list of drugs and specific clinical situations that set an opportunity for deprescribing when both of them are present in a PMM, and create a tool suitable for clinical practice. It had to contain situations in which an appropriate drug become inappropriate and indications to monitor the patient after drug withdrawal, qualities that made it different from STOPP and the Beers criteria.

Methods

The study was carried out using Delphi methodology, combining the synthesis of scientific evidence with the opinions of experts.[17]

Development of criteria: Literature review and electronic brainstorming

A literature review on MedLine and EMBASE (June to September 2013) was carried out to identify deprescribing models and papers on deprescribing in chronic patients. Specific drugs and specific clinical situations for which deprescription have been tested were identified (Fig. 1). Qualitative and quantitative studies, theoretical and clinical studies, original studies, and reviews were included. The references of the selected documents were reviewed manually. From all identified criteria of deprescribing, the researchers selected those of possible use for PMM, based on the following:

1. They were developed for PMM or very similar patients (chronic, elderly with comorbidities, polymedicated etc.).
2. They were validated or, alternatively, widely used in clinical practice, and had at least a quality fieldwork study.

Articles were included if they described, at least: drug/s for which withdrawal takes place and type of intervention. Studies carried out on patients with acute diseases, those who spoke languages other than Spanish and English, and those where the entire text could not be recovered were excluded.

Duplicate articles were removed, and a selection was made by title and abstract (by authors ARP and ERAL), reviewing the entire text in case of doubt. A third researcher (BSR) resolved discrepancies.

Electronic brainstorming was also carried out to maximize group productivity.[18] The working team consisted of internal medicine specialists and hospital pharmacists. They were recruited from the chronicity-related special interest groups of their scientific societies. Electronic brainstorming was designed in two rounds: in the first round, a list was required to be filled in with: clinical situations that could be considered opportunities for deprescribing, clinical variables for follow up, time follow up, prognostic relevance (yes/no) and scientific evidence. In the second round, participants were asked to modify or complete the information that investigators had sent back after processing and removing duplications. They were asked to include evidence in each new criterion they provided or to indicate if there were situations they usually had with their patients and that had been managed with the proposal provided.

So the final criteria were selected from the aforementioned two processes (literature review and electronic brainstorming). Each criterion was built by four features: (i) drug indication for which the drug was prescribed; (ii) specific clinical situation that offered the opportunity to deprescribe the drug; (iii) health variables that would be monitored to assess the impact of deprescribing on patient's health; and (iv) follow up: the minimum time that the patient's health variables would have to be monitored. These features were obtained from the variables measured in the clinical trials or reviews found of each specific drug and the information obtained by the brainstorming.

Expert panel

The group of experts consisted of 11 members, six of whom were women. Participants included four specialists in hospital pharmacy, three in internal medicine, three general practitioners and one primary care pharmacist. They were from six different Spanish regions. Likewise, the panel was composed of six experts in PMM and five

1. (aged or older or elder* or polypatological or multimorbidity).ti,ab.

2. ((drug? or medication? or medicine? or treatment? or prescribing or polypharmacy) adj3 (stop* or discontinu* or withdraw* or deprescrib* or cease or cessation)).ti.

3. 1 and 2

4. Limit 3 to (English or Spanish)

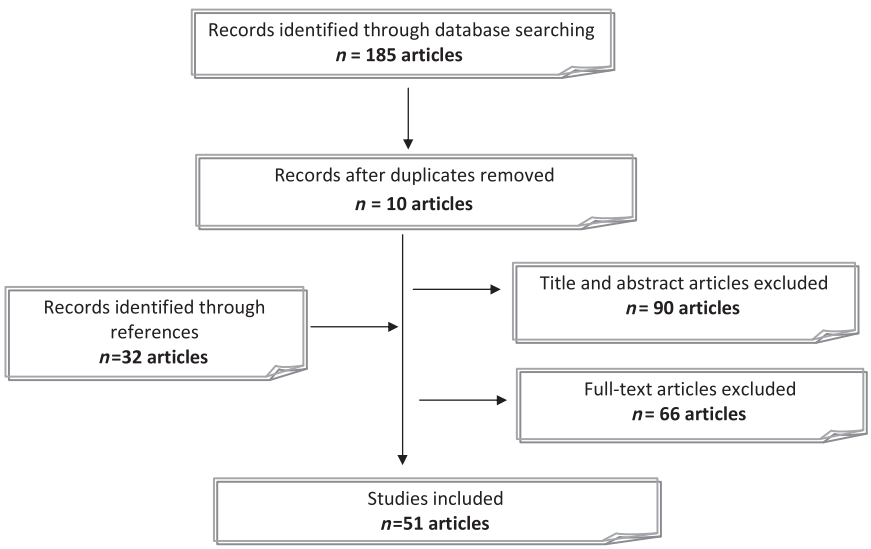

Figure 1 Search strategy and PRISMA flow diagram of the literature review.

experts in pharmacology. For recruitment, members were contacted by telephone, and provided with information on the study objective, possible workload and schedule. Once they accepted, they were sent a communication agreement.

There were two online consecutive rounds. In the first round, the experts received the questionnaire with the list of criteria and two articles that summarized the most representative evidence of deprescribing.[9,19] They were asked to rate each criterion (from 1 to 9 points) for the following three features in order to appraise the appropriateness for deprescribing action: (i) strength of evidence; (ii) usefulness in PMM; and (iii) applicability in clinical practice.

In the second round, each panel member received a personalized sheet with their previous vote, the results of the panel assessment in each criterion (median of the scoring, its scoring in the first round and range of the scoring obtained) and all suggestions made anonymously during the first round.

Criteria were classified into three levels of appropriateness and agreement, following the definitions of the methodology.[17]

Creation of the tool

Afterwards, the research group organized a meeting to carry out the critical assessment of the result for the definitive selection of criteria to be included in the tool. Those criteria that were considered appropriate in agreement between experts at least in two of the three criteria rated were included. Those considered inappropriate were not included. The uncertain criteria or those with disagreement were deeply discussed and contrasted with the evidence found. Another important issue to be discussed was the convenience of including the life prognosis (according to the PROFUND index) in every criterion of the final tool.

The design of the tool and its name were also decided.

Results

Literature review and electronic brainstorming

The literature review provided 51 articles, neither of them referred to PMM specifically. Most articles were controlled trials of deprescribing a unique or narrow spectrum of drugs in small populations of institutionalized patients or

in the context of general practice. The most represented drug class was biphosphates, followed by benzodiazepines and neuroleptics. Most drugs were developed in Europe and the USA.

The invitation for the brainstorming was accepted by 63 professionals from different places in Spain, 19 specialists in internal medicine and 44 in hospital pharmacy. After both rounds, 74 different criteria were identified. Criteria referring to specific drugs of a group were clustered together in drug classes. The information obtained by the brainstorming was completed and contrasted with the results and variables of evidence found in the literature review.

After the study of these data, 100 criteria were elaborated to be evaluated by the expert panel. These criteria consisted of two cases per each of 50 different clinical situations, each case corresponding to one extreme situation regarding life prognosis according to the PROFUND index, namely >11 points and below <11 points, respectively. They were structured into seven sections ordered according to the anatomical level of the ATC classification system. Thus, there were 18 criteria that included drugs for the alimentary tract and metabolism (chapter 1), 16 for blood and blood-forming organs (chapter 2), 28 for the cardiovascular system (chapter 3), eight for the genitourinary system/systemic hormonal preparations (chapter 4), 10 for the musculoskeletal system (chapter 5), 18 for the nervous system (chapter 6) and eight for the respiratory system (chapter 7).

Expert panel

All the experts completed the first round, whereas nine completed the second round (Fig. 2).

Globally, according to the three items rated, there were five criteria that were considered as inappropriate in more than one item. The scores hardly changed when considering patients with worse prognosis, except for one criterion that referred to oral anticoagulants.

Creation of the tool

The research group discussed the criteria that were rated as uncertain. Finally, 27 criteria were selected for creating the List of Evidence-baSed depreScribing for CHRONic patients criteria (LESS-CHRON; Table 1).

The life prognosis was included in one criterion of the tool, as a necessary condition for deprescribing.

Discussion

To our knowledge, the LESS-CHRON criteria constitute the first explicit tool to assist clinicians in deprescribing in PMM.

The drugs included in LESS-CHRON criteria are in concordance with previous studies of deprescribing. A systematic review of withdrawal trials in older adults showed the feasibility of discontinuing antihypertensive agents, psychotropic drugs and benzodiazepines.[19] Another systematic review of ceasing medication identified a wide variety of drugs: benzodiazepines, other psychoactive drugs, metformin, antibiotics, proton pump inhibitors, opioids and hormone replacement therapy.[20] One more recent review found evidence in diabetic therapy, bisphosphonates, benzodiazepines and acetylsalicylic acid, among others.[21]

The methodology developed to create the LESS-CHRON criteria was similar to other explicit criteria tools in the context of improving medication use (for instance, STOPP/START and Beers criteria): the Delphi consensus technique.[22,23] Furthermore, our research group previously used this methodology to identify and select the most appropriate tools for measuring treatment compliance and appropriateness in PMM patients.[24]

There are two previous experiences in deprescribing that used expert panel methodology. In the first, the panel compared the concordance between clinical practice and the application of a new guideline of deprescribing (OncPal Deprescribing Guideline) in the identification of potentially inappropriate medicines in palliative cancer patients.[16] The second was a modified Delphi process to find priority drug classes to be included in deprescribing guidelines for older adults. It consisted of three rounds or surveys involving 64 participants. It should be emphasized that most of the drugs finally selected as priorities are actually included in the LESS-CHRON criteria.[25]

The structure of the LESS-CHRON criteria is similar to the known STOPP/START criteria, organized by physiological systems. Updated Beers criteria and "OncPal Deprescribing Guideline" are also structured in the same way.

Deprescribing, since its first appearance in the literature in 2003, has developed enormously, but mostly in a theoretical way.[9] A review showed that there is a lack of consensus in its definition and in its international generalizability.[26] Recently, a deprescribing five-step protocol by the Australian Deprescribing Network has been developed: the CEASE deprescribing framework (Current medication, Elevated risk, Assess, Sort, Eliminate).[12,13,27–29] Authors of CEASE consider that they are necessary more prediction tools, evidence tables an decision aids to achieve the implementation of the deprescribing process in clinical practice.[12,13] The LESS-CHRON criteria would be useful for physicians to select which patients can benefit from deprescribing (those who are taking the drug in the clinical situation that the tool indicates), and to discuss the deprescribing plan with them at the medical consultation. It is crucial to know patient's preference before applying the criteria. Furthermore, the LESS-CHRON criteria might spread the concept of deprescribing as well as contribute to its development beyond native English-speaking countries.

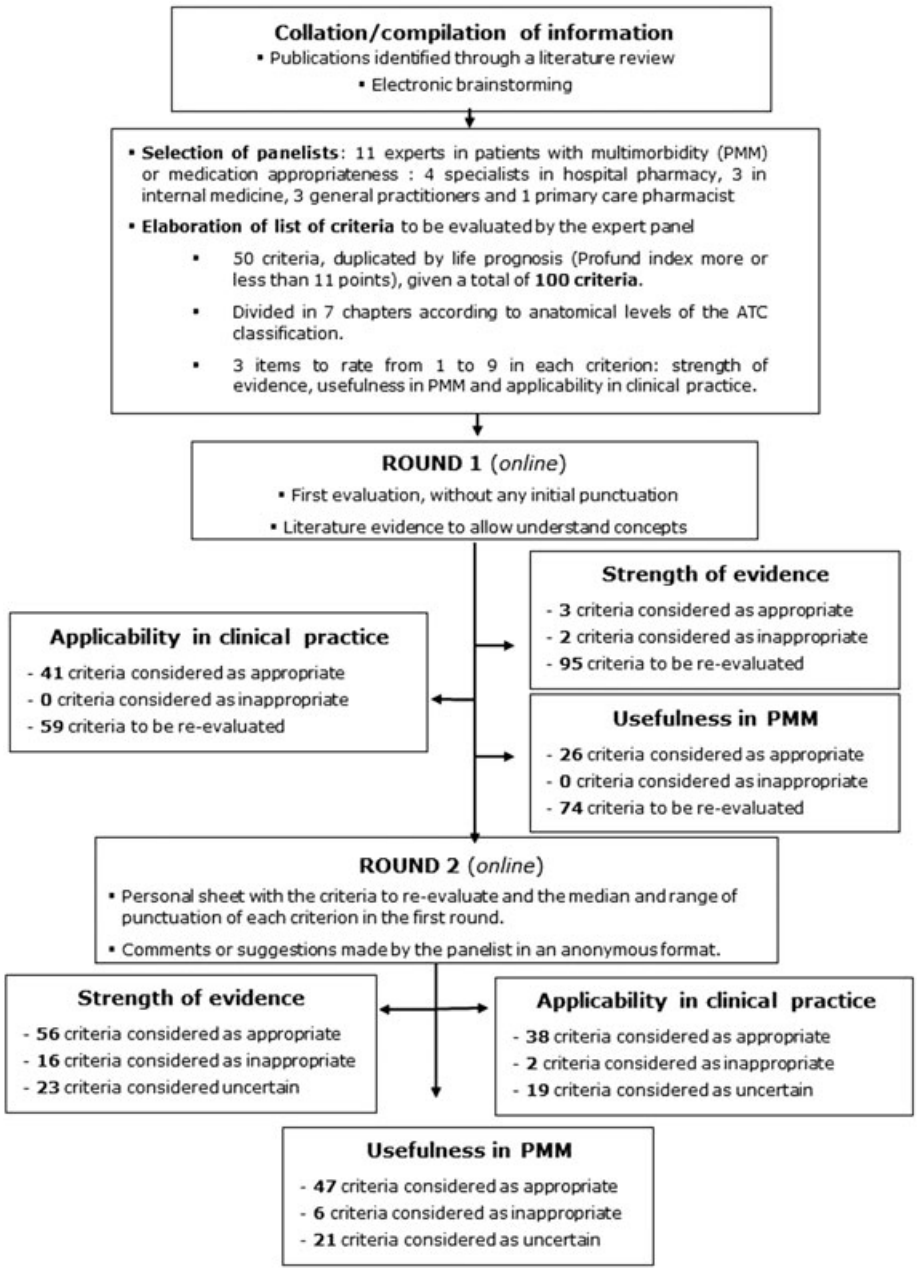

Figure 2 Delphi process. Development of the criteria and main results for the three items evaluated in each round. ATC, Anatomical, Therapeutic, Chemical classification system; PMM, patients with multimorbidity.

Another strength of the LESS-CHRON criteria is that it has been built up by a team of pharmacists and physicians, from hospital and primary settings. This multidisciplinary approach might be useful to overcome the known barriers of deprescribing.[30]

Some of the limitations of this work were: that nurses were not included on the expert panel, and the limited number of experts compared with the other Delphi method carried out in the context of deprescribing.[25]

We expected to obtain differences in the scores according to life prognosis. Maybe experts did not understand the Delphi in this aim. Many of them considered that the approach to patients with a PROFUND index score of >11 should be mostly palliative, and different from the deprescribing criteria they were grading.

Some criteria of the final list were not based on solid evidence, as they emerged from the brainstorming. It could be the main limitation of the present study. Our research group has carried out an inter- and intrareliability study to validate the LESS-CHRON criteria. Conscious of the importance of its clinical

Table 1 List of Evidence-Based Deprescribing for Chronic Patients (LESS-CHRON) criteria

Drug	Indication for which it is prescribed	Deprescribing condition	Health variables to monitor	Follow up
Alimentary tract and metabolism				
Oral diabetic agents, except metformin	Type 2 diabetes	Aged ≥80 years (frail) Diabetes of >10-year evolution in treatment with insulin	HbA1c <8.5%	3 months
Acarbose	Type 2 diabetes	More than one drug for diabetes treatment. Well controlled diabetes.	HbA1c <8.5%	3 months
Metformin	Type 2 diabetes	Low body mass index. Under treatment with insulin	Weight variations	3 months
Calcium/vitamin D supplement	Prophylaxis for fractures	Patient unable to walk and Barthel Index <60	New fracture	Not applicable
Blood and blood-forming organs				
Oral anticoagulants	Atrial fibrillation	Pfeiffer questionnaire ≥8 points and PROFUND index ≥11 points.	Not applicable	Not applicable
		High risk of falls.	Not applicable	Not applicable
Acetylsalicylic acid	Primary prevention	Age as only risk factor	Acute coronary syndrome	Not applicable
Clopidogrel + acetylsalicylic acid	Post-acute oronary syndrome prevention	More than 1 year of dual antiplatelet therapy. Withdraw one of them.	Acute coronary syndrome	3 months
Cardiovascular system				
Antihypertensives	High blood pressure	Patients aged >80 years with systolic blood pressure <160 mmHg and more than one antihypertensive drug. Withdraw an antihypertensive drug not considered as first-line treatment.	Blood pressure values	3 months
Statins	Primary prevention	Aged ≥80 years	Cardiovascular events	Not applicable
	Secondary prevention	Pfeiffer questionnaire ≥8 points	HDL/LDL levels	Not applicable
Nimodipine	Prophilaxis for neurological deterioration	Long-term treatment (≥1 year)	Cognitive impairment	3 months
Genito-urinary system				
		Use of nappy.		
Anticholinergics	Urinary incontinence	Worsening of dementia symptoms in patients under anticholinesterase treatment.	Urine control	1 month
Alpha-adrenergic blockers	BPH	Asymptomatic patient or with symptoms that do not affect the patient's quality of life	BPH symptoms	2 months
Allopurinol				

(*Continues*)

Table 1 (Continued)

Drug	Indication for which it is prescribed	Deprescribing condition	Health variables to monitor	Follow up
	Secondary prevention	>5 years free of gout episodes	Gout episode	Not applicable
Musculo-skeletal system				
Bisphosphonates	Primary prevention	5-year treatment	New fracture	1 year
	Secondary prevention	Patient unable to walk	New fracture	6 months
Nervous system				
Haloperidol Risperidone Quetiapine	Delirium during hospitalization	After a month's behavioral stability	Changes in behavior. Agitation	1 month
Benzodiazepines	Anxiety	Absence of anxiety in the previous month	Monitoring components of anxiety	1 month
Benzodiazepines Z drugs (Zolpidem/Zoplicone/ Zaleplone)	Insomnia	Absence of insomnia in the previous month	Sleep monitoring	1 month
Antidepressants	Reactive depression	Basal mood recovery after at least 6 months of treatment	Recurrence of depressive symptoms	2 months
	Behavioral alteration Alzheimer's disease	Advanced Alzheimer's disease GDS >6.	Agitation Behavior alterations	2 months
Anticholinesterases	Alzheimer's disease	In combination with memantine: withdraw one of them. Patients with advanced Alzheimer's disease (GDS >6) or no response to treatment in the previous year	Agitation Behavior alterations	2 months
Citicoline	Vascular dementia	Pfeiffer questionnaire >8 points	Cognitive and functional assessment	3 months
Respiratory system				
Mucolytics and expectorants	Bronchopulmonary disease	Stability in underlying disease	Mucus, respiratory capacity	1 month

BPH, benign prostatic hypertrophy; GDS, Geriatrics Depression Scale; PROFUND.

validation, there is a work in progress in the collaboration between the Spanish Society of Internal Medicine and the Spanish Society of Hospital Pharmacy to develop a deprescribing clinical trial by using the LESS-CHRON criteria.

As every explicit criteria worldwide, this first version of the LESS-CHRON criteria needs to be updated whenever necessary. Furthermore, it is a reality that nowadays the routine clinical practice is computerized. Prescription support tools are usually online, in a web or app format. Therefore, our research group works on an electronic platform in which it will be possible to consult the criteria and evidence, and share experiences with other professionals.

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Disclosure statement

The authors declare no conflict of interest.

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