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Prevalence of PIM in patients with multimorbidity according to LESS-CHRON and STOPPFrail criteria

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Abstract:	Abstract Objective: LESS-CHRON and STOPPFrail are criterion-based deprescribing tools. This study aimed to identify the prevalence of potentially inappropriate medications (PIM) with these tools in an outpatient, polymedicated, older population with multimorbidity. Design: Single-center cross-sectional observational study. Setting and Participants: PIM and criteria subject to deprescribing identified by each tool were collected in patients who were being followed up on outpatient internal medicine consultation. Methods: PIM were identified by STOPPFrail and LESS-CHRON criteria reviewing medical histories and pharmacological treatments of the patients in the electronic health card system. Sociodemographic, clinical and pharmacological variables were recorded. A correlation analysis between treatment tools and clinical values was performed using the non-parametric Spearman's Rho correlation. Results: Eighty-three patients with a median of 14.4 (12;17) prescribed drugs were included. The total number of PIM identified with LESS-CHRON was 158 vs. 127 with STOPPFrail. Eight of the 27 criteria (29.6%) for LESS-CHRON and 15 of the 25 for STOPPFrail were found to be not applicable. A significant correlation was obtained for both tools with the number of prescribed drugs at the time of inclusion. The Profund, Barthel, and VGI-index only showed a significant correlation with LESS-CHRON. Conclusion and Implications: Both tools have shown the capacity to identify PIM that can be deprescribed in the population studied. However, LESS-CHRON appears to have a greater detection potential in the subgroup of patients analyzed. STOPPFrail brings a certain complementarity in other areas of therapy not covered by LESS-CHRON.

08/08/2022

I am writing as author of correspondence of the manuscript titled **"Prevalence of PIM in patients with multimorbidity according to LESS-CHRON and STOPPFrail criteria.".**

This manuscript compares the detection potential of the STOPPFrail criteria versus LESS-CHRON as screening tools in a cohort of polymedicated elderly patients with multimorbidity. We analyse the ability of these tools to identify inappropriate drugs in this population, as well as the therapeutic groups most frequently involved in the deprescription opportunities detected.

In addition, the evaluation of the correlation between the different deprescription criteria identified, the deprescription opportunities and the applied clinical scales was carried out.

This work highlights the theoretical usefulness of two deprescription tools that are very well positioned in the scientific literature.

This work is not under active consideration for publication, has not been accepted for publication, nor has it been published, in full or in part (except in abstract form). I confirm that the study has been approved by the Ethics Committee of Virgen del Rocío University Hospital, an institutional ethics committee
For all this we remain attentive to your response. If you need any further information, do not hesitate to contact me.

We explicitly state that:

(1) the manuscript has not been and will not be submitted, in part or entirety, elsewhere for publication;
(2) all authors meet criteria for authorship as stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (explained below), as well as their contributions to the manuscript;
(3) if accepted, the paper will not be published elsewhere in the same form, in English or in
any other language, including electronically, without the written consent of the copyright holder;
(4) the instructions for authors have been taken into account, including that all signatory authors meet the requirements of authorship and declare that they have no conflict of interest.

In addition, a list of three potential reviewers for our manuscript are described:

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Regards,

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7th November 2022

Dear reviewers:

We deeply appreciated the exhaustive review and the contributions raised in our work presented in the manuscript *Prevalence of PIM in patients with multimorbidity according to LESS-CHRON and STOPPFrail criteria (JAMDA-D-22-00659)*.

The corrected version of the manuscript with the modifications, made and indicated with "track changes" has been send.

Below are our comments for the reviewer. We hope we have addressed all issues raised by the reviewer. However, do not hesitate to contact us if the need further information.

REVIEW 2:

1. **Reviewer #2: Thanks to the authors for the revised manuscript. The responses that describe how STOPPFrail and LESS-CHRON are implemented and how to interpret the figures are particularly helpful, and I would recommend adding a supplemental appendix to describe the circuit (although I defer to the editor—perhaps this isn't necessary for the JAMDA audience).**

Following your recommendations, we have included the circuit carried out as supplementary material (S3). If the editor considers it necessary to include also the interpretation of the figure, we add it without problems.

2. **The organization of the Discussion section is helpful as well, which I think would benefit from a discussion of the fixed costs of the two platforms so that readers could have more context for deciding which one to implement.**

Thank you very much, certainly the changes in the discussion have improved the article.

Regarding the issue of costs, the truth is that, to the best of our knowledge, there is no web platform available for the STOPPFrail criteria, just the original article with the criteria is published. In the case of LESS-CHRON, it is available in web format (https://chronic-pharma.com/) and it is free.

We have not added anything in this regard because the authors consider that both are easy to apply since they are available (supplementary material S1 and S2 of this manuscript). Adding this information perhaps benefited LESS-CHRON excessively and did not seem entirely fair to us. Despite this, we have added a sentence to the discussion in this regard:

First of all, it is important to mention that both tools are available in the scientific literature without any associated costs.

3. **I am still concerned with selection bias and the possibility that the study sample mechanically increase the likelihood that LESS-CHRON dominates in the head-to-head. However, I recognize that the authors are limited in space and may not be able to conduct more rigorous analysis given the setting and statistical power. I was confused by the authors' statement in the response document that their sample is representative, which lacked evidence, and their claim that they are "avoiding selection bias," which is impossible.**

We are sorry for the misunderstanding, perhaps we did not express ourselves correctly in the previous letter.

It is true that if we do not randomize, bias is more likely to occur. However, our sample is representative of chronic complex patients because the entire sample has these characteristics, and the appropriate sample size is reached according to the calculation performed: "*To achieve a correlation coefficient other than 0 and an r of at least 0.30, assuming a type I error of 0.05 and a type II error of 0.20, it was necessary to include at least 80 subjects in the study*". In other words, we tried to indicate that the inclusion of 83 patients represents a sufficient sample in terms of statistical power.

In addition, the main objective of this study was to compare the potential theoretical applicability of these tools in a population on which we can routinely make pharmaceutical interventions. Therefore, while we understand your concern, we believe that we have not committed any significant bias. As we mentioned earlier, when we reviewed candidate patients, we included all those who had any potential PIM for any of the tools evaluated. Therefore, there are patients who only have applicable PIM for STOPPFrail and not for LESS-CHRON. Thus, when applying theoretically and simultaneously both tools to each patient, if STOPPFrail would have had a very different potency than LESS-CHRON, this would be reflected in these results.

4. **The authors then state that "both tools are perfectly comparable in terms of methodology and design" but describe reasons why they are not comparable.**

Indeed, perhaps the statement is contradictory, we explain.

We are referring to the fact that, as has been demonstrated in previously published works, both tools have been shown to be comparable in terms of methodology and design (10.1016/j.sapharm.2022.03.008; 10.1111/jgs.15616). That is, both are explicit criteria, focused on elderly patients, with the objective of deprescribing drugs (not focused on appropriateness), designed by a panel of experts following a Delphi methodology, organized by therapeutic groups, etc.

However, this does not exempt that there are other aspects that slightly differentiate them, such as the fact that STOPPFrail includes two not explicit criteria (section A), which were eliminated. Nevertheless, as we mentioned in the previous letter, it is common to find articles in the literature comparing tools that are somewhat different from each other (LESS-PHARMA Study), which does not mean that it cannot be done as long as it is properly discussed as we have done.

However, our objective is to compare the detection potential of both tools and to describe the main differences and similarities, which may logically influence the applicability of each one, but hence the value we intend to contribute with this work.

5. **It also appeared that the authors de-emphasize that STOPPFrail is specifically geared toward frail adults in the introduction.**

Totally, we have deleted it from the previous version in an attempt to simplify. We have added it again:

On the other hand, STOPPFrail is specifically geared toward older frail patients. This tool also takes into account clinical conditions to perform deprescribing, although it does not specify out health variables or monitoring parameters[15].

Prevalence of PIM in patients with multimorbidity according to LESS-CHRON and STOPPFrail criteria

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Running title: Prevalence of PIM according to deprescribing tools

Key words: LESS-CHRON; STOPPFrail; deprescribing; older patients; multimorbidity; polymedicated.

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Word, reference, and graphics count: 2630 words, 22 references, 3 tables and 1 figure.

Brief summary: Inappropriate medication is highly prevalent among elderly and chronic patients. Deprescription tools have been development as strategies to identify it. Studies detecting potentially inappropriate medications are necessary.

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Prevalence of PIM in patients with multimorbidity according to LESS-CHRON and STOPPFrail criteria

Abstract

Objective: LESS-CHRON and STOPPFrail are criterion-based deprescribing tools. This study aimed to identify the prevalence of potentially inappropriate medications (PIM) with these tools in an outpatient, polymedicated, older population with multimorbidity.
Design: Single-center cross-sectional observational study.

Setting and Participants: PIM and criteria subject to deprescribing identified by each tool were collected in patients who were being followed up on outpatient internal medicine consultation.

Methods: PIM were identified by STOPPFrail and LESS-CHRON criteria reviewing medical histories and pharmacological treatments of the patients in the electronic health card system. Sociodemographic, clinical and pharmacological variables were recorded. A correlation analysis between treatment tools and clinical values was performed using the non-parametric Spearman's Rho correlation.

Results: Eighty-three patients with a median of 14.4 (12;17) prescribed drugs were included. The total number of PIM identified with LESS-CHRON was 158 vs. 127 with STOPPFrail. Eight of the 27 criteria (29.6%) for LESS-CHRON and 15 of the 25 for STOPPFrail were found to be not applicable. A significant correlation was obtained for both tools with the number of prescribed drugs at the time of inclusion. The Profund, Barthel, and VGI-index only showed a significant correlation with LESS-CHRON.
Conclusion and Implications: Both tools have shown the capacity to identify PIM that can be deprescribed in the population studied. However, LESS-CHRON appears to have

a greater detection potential in the subgroup of patients analyzed. STOPPFrail brings a certain complementarity in other areas of therapy not covered by LESS-CHRON.

Introduction

Advances in social health status translate to an increase in life expectancy and therefore progressive population aging, leading to a greater prevalence of chronic diseases[1,2]. These results are in the interrelated concepts of chronic complex patients or patients with multimorbidity and frail patients[3,4].

Patients with multimorbidity are defined as those patients who suffer from two or more long-term conditions[5]. In our setting, this definition was agreed on in the Integrated Care Process for Patients with Multimorbidity (ICPPMM), establishing a series of clinical categories to define these patients[6] to homogeneously identify them. As a result, this population is characterized as complex, with high mortality, dependence, limited functionality, and vulnerability[7]. Furthermore, most of these patients are polymedicated[8].

Due to the complexity in managing treatment in these patients, specific strategies are necessary to optimize pharmacological therapy for these patients. These consist of interventions to improve appropriateness, generally of a multidisciplinary nature[9], which manage to reduce drug-related problems and optimize costs derived from health care[10].

Deprescribing has recently been included as a relevant strategy in this type of patient, with good results[11]. It is a process to review and evaluate long-term therapeutic plans in order to withdraw, substitute or reduce the dose of those drugs that, under certain clinical conditions, could be considered unnecessary or have an unfavorable benefit-risk ratio[12].

There are numerous strategies to carry out deprescribing. According to the systematic review conducted in 2019[13], the two most ideal explicit tools for application in clinical practice and identification of potentially inappropriate medications (PIM) in older patients are LESS-CHRON[14] and STOPPFrail[15].

Both are criterion-based tools developed by an expert panel, who reached a consensus on the deprescribing scenarios to be included according to bibliographic evidence. For their part, the LESS-CHRON[14] criteria were designed for patients with multimorbidity or those with similar characteristics and were based on four basic aspects: the indication for which the drug is prescribed, the condition that allows deprescribing, the health variables to monitor and the follow-up time during which different health variables must be monitored. On the other hand, STOPPFrail is specifically geared toward older frail patients. This tool also takes into account clinical conditions to perform deprescribing, although it does not specify out health variables or monitoring parameters[15].

Although the STOPPFrail tool appears to be the most appropriate to be used in outpatients with multimorbidity under certain clinical conditions[6], the truth is that there are currently no studies comparing both tools. Therefore, the aim of this study was to identify the prevalence of PIM in this group of patients and to compare the detection potential of LESS-CHRON criteria to those of STOPPFrail as screening tools in this population.

Materials and Methods

This project was carried out at a reference university hospital located in Spain. The design consisted of a unicentric cross-sectional observational study with recruitment taking place between October 2020-April 2021.

Participants

Patients who were being followed up on outpatient internal medicine consultation were included. The following were the inclusion and exclusion criteria:

Inclusion criteria

89 • Polymedicated (>5 active drugs) and ≥65 years patients who provided informed
90 consent.

91 • Patients with multimorbidity or, in its absence, complex chronic patients[6].

92 • Patients who are undergoing treatment with at least one drug for the indication listed
93 in one of the two tools being evaluated.

94 Exclusion criteria:

95 • Patients with unstable active malignant neoplasm and disseminated metastasis.

96 • Patients with neurological or mental disability without a legal representative.

97 • Patients in a clinical state of agony.

98 *Procedure and study variables*

99 Medical histories and pharmacological treatments of the patients were recorded in the
100 electronic health-card system. PIM were identified by STOPPFrail and LESS-CHRON
101 criteria. The LESS-CHRON tool includes 27 deprescribing criteria, considering the
102 pairing indication-clinical situation offering the opportunity for deprescribing to be a
103 criterion (Supplementary material S1). On the other hand, although the STOPPFrail tool
104 is also based on 27 criteria (Supplementary material S2), two of them focus do not specify
105 drugs with concrete withdrawal proposals, that is, they are not explicit criteria (Section
106 A)[16]. Therefore, taking this into account, the above, a modified version of STOPPFrail
107 was used to compare drug lists with specific indications. Each criterion of the tools allows
108 to identify one or more PIM. The circuit that was carried out is shown in Supplementary
109 material S3.

110 To respond to the objectives of the study, the following variables were recorded:

- Sociodemographic.
- Clinical:
  - Categories that identify patients with multimorbidity (Supplementary material S4)
  - Main comorbidities
  - Cognitive decline (Pfeiffer index)[17]
  - Functional decline (Barthel index)[18]
  - Prognostic stratification (Profund index)[19]
  - Frailty (Frail-VIG index)[20]
- Pharmacological:
  - Number of prescribed drugs at the time of inclusion.
  - Number of PIM detected.
  - Number of deprescribing criteria applicable.
  - Main active agent or pharmacological group to which each of the PIM belongs.

Analysis

Data description was carried out using frequencies for qualitative variables and median and IQR for quantitative variables because they were not distributed following a Normal distribution. The correlation between deprescribing criteria, pharmacological treatment and clinical variables was evaluated using the non-parametric Spearman's Rho correlation. All of the analyses were carried out using the statistical software Jamovi version 1.6.23.

To achieve a correlation coefficient other than 0 and an r of at least 0.30, assuming a type I error of 0.05 and a type II error of 0.20, it was necessary to include at least 80 subjects in the study[21].

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of XXX. Informed consent was obtained from all subjects involved in the study.

Results

Of all the patients who agreed to participate in the study, 83 patients met all inclusion criteria and then were included in the study. However, certain clinical variables were not recorded in some patients as reflected in Table I.

Demographic, pharmacological, and clinical characteristics

Of the patients analyzed, 81.5% did not show cognitive decline according to the Pfeiffer questionnaire. Similarly, the median of Barthel index showed slight dependence, ranging from 60 to 95 points, in 52.4% of the patients. In addition, the median obtained with the Profund index suggested a low-intermediate risk (21.5-31.5%) of death at one year after hospital discharge in 33.7% of the patients and an intermediate-high risk (45-50%) in 25.3%. The patient cohort showed mild frailty, but near the upper limit (mild frailty 0.2-0.36 and moderate frailty 0.39-0.53).

Based on established inclusion criteria, the population studied had a high prevalence of chronic disease. Thus, the median number of clinical categories presented was 3 (3;4). The most frequent clinical categories were heart failure (63.9%), chronic kidney disease (55.4%), anemia from gastrointestinal loss (48.2%), chronic respiratory disease (39.8%),

and ischemic heart disease (30.1%), respectively. With regard to the comorbidities recorded, the most common were arterial hypertension (88%), dyslipidemia (60.2%), atrial fibrillation (48.2%), and diabetes mellitus without complications (45.8%).

Assessment deprescribing with the LESS-CHRON and STOPPFrail tools

Regarding pharmacological treatment, as has already been commented, the median number of prescribed drugs per patient was 14.4 (12;17). The total number of PIM and deprescribing criteria identified with both tools are shown in Table 2. No significant differences were detected between the tools.

Of the cohort studied, 10.8% of patients (n=9) did not meet any deprescribing criteria for the LESS-CHRON tool and 13.3% (n=11) did not for the STOPPFrail tool.

The prevalence of PIM according to deprescribing criteria of each tool is presented in Figure 1.

In LESS-CHRON, 8 of the 27 criteria (29.6%) were found not to be applicable to any patient. The most prevalent criterion was withdrawal from benzodiazepine for insomnia (F3), with a value of 31%, followed closely by the deprescribing of antidepressants (F4) in the case of reactive depression (27%). In the case of STOPPFrail, 15 of the 25 criteria (60%) were not used and the withdrawal criterion of the lipid-lowering therapy (B1) was the most theoretically applied, present in 69% of patients.

Correlation analysis between pharmacological and clinical variables in both tools

A weak correlation between both tools was observed (29.5%, p=0.007 with respect to the criteria; 29%, p=0.008 with respect to the PIM for deprescribing) (Table 3A). As far as the correlation between the prescribed drugs in the population at the time of inclusion,

176 although there is a correlation in both tools, this was found to be greater in LESS-
177 CHRON.

178 Table 3B shows that none of the clinical indexes correlated with the STOPPFrail tool.
179 However, the Profund, Barthel, and frailty indexes did show a significant correlation with
180 LESS-CHRON for both the criteria variable and PIM for deprescribing.

181 **Discussion**

182 *Population target*

183 This study, which is the first to compare LESS-CHRON and STOPPFrail tools, confirms
184 that both explicit tools can be used to detect PIM in frail patients or those with a limited
185 life expectancy[13]. This is based on the fact that 77% of patients (n=64) met a minimum
186 of one deprescribing criterion in both tools. These results are consistent with the literature
187 and show the usefulness of deprescription tools in supporting the process[16, 22]. However,
188 the LESS-CHRON tool was found to have greater detection potential due to a higher
189 number of PIM obtained, and the correlation of the tool with pharmacological and clinical
190 parameters.

191 The differences found could be due to the target population towards which both tools are
192 directed. In this sense, the STOPPFrail authors geared the tool towards frail patients with
193 a life expectancy less than one year[15]. However, LESS-CHRON was designed to be
194 applied in chronic patients with multimorbidity or those with complex health needs[14],
195 which does not necessarily imply a short survival prognosis. In fact, survival prognosis is
196 included in this tool as a variable to consider in different proposed deprescribing criteria.

197 The cohort analyzed in this study is older, with a high degree of polymedication and
198 comorbidities. However, in terms of prognosis, the Profund index obtained implies a low-

intermediate risk of mortality at 12 months and Frail-VIG index indicates that elevated mortality at 1 year cannot be presumed[19, 20].

Theoretical applicability of the tools

Taking into account the theoretical applicability of the tools, combined to the fact that STOPPFrail[15] incorporates laxer withdrawal criteria, it could be expected that the number of PIM detected with this tool is greater than with LESS-CHRON. However, the results obtained show the opposite. This could be the consequence of a greater suitability of the LESS-CHRON criteria for this population or the tool having a greater sensitivity for the type of the prescribed medication in these patients. In this way, although the criteria of the STOPPFrail tool are more flexible, if the patient is not clearly at the end of their life, the application may be somewhat complex. This, together with the elimination of section A, could determine the lower detection capacity of PIM compared to previous studies of this tool[23].

Differences according to the functional system

In line with the criteria for each tool according to the drug involved, the differences according to the functional system can be analyzed. Consequently, the most notable is found in the systems or groups of drugs that are only represented in one of the tools. Specifically, in the case of STOPPFrail, the criteria related to the gastrointestinal tract (PPI and H2 antagonists), which make up 21% of the total, and in the case of LESS-CHRON, the group of benzodiazepines, Z drugs, and antidepressants (46% of the total), together with the scenario that suggests the deprescribing of allopurinol in the secondary prevention of gout (11%). In fact, they can be considered the criteria with greatest complementarity between both tools, representing a high percentage of the total criteria identified (40.8%).

Similarities between LESS-CHRON and STOPPFrail

First of all, it is important to mention that both tools are available in the scientific literature without any associated costs.

Regarding the similarities identified, it is striking that they share 10 of the same criteria, although they slightly differ with respect to the clinical situation that allows for deprescribing. If the criterion referring to lipid-lowering therapies is specifically analyzed, it is the most applied in STOPPFrail (46% of the total), this figure is not maintained for LESS-CHRON since this tool establishes more restrictive conditions. The same is true for the third most prevalent criterion in STOPPFrail, where general withdrawal of calcium supplements is advocated, while LESS-CHRON specifies that patients must have a Barthel index <60 and be unable to walk, again creating differences in applicability (20% vs. 7%). In the opposite situation, the criterion indicating the deprescribing of alpha-blockers in prostatic hypertrophy is highly prevalent in LESS-CHRON, while in STOPPFrail, withdrawal was only recommended when the patient was catheterized. Finally, in the endocrine system, both tools indicate the withdrawal of oral antidiabetics, but due to differences in clinical conditions, the prevalence in LESS-CHRON is 14% vs. 8% in STOPPFrail.

Another relevant finding is that although the number of criteria analyzed for each tool was similar (27 in LESS-CHRON and 25 in STOPPFrail), it is true that in STOPPFrail only two criteria made up 65% of the total (criteria B1 and E1) and one of them affected 70% of the patients (criterion B1). However, in LESS-CHRON, the application of the different items was more homogeneous, distributed over a greater number of different criteria, and the sum of the three most applied criteria was less than 50% of the total.

It should be note that while this study was conducted, a new version of the STOPPFrail tool was published[24], which incorporates new criteria and eliminates others that had become obsolete. Nevertheless, none of the previously mentioned criteria that carried considerable weight in LESS-CHRON have been added in the new version.

Finally, it is important to mention that both tools consider criteria did not detect any candidate drug to be withdrawn, with a higher number in STOPPFrail compared to LESS-CHRON (15 vs 8 criteria). However, after the update to the English version of STOPPFrail[17], 6 of those 15 criteria have been eliminated, while 2 of them have been modified. With respect to LESS-CHRON, a study is currently underway to validate the criteria in a cohort of institutionalized patients and outpatients. With this study, data on usability and clinical utility will be obtained that will allow the criteria to be adapted to actual use needs.

In assessing the correlation between the clinical parameters, it is worth noting that neither the number of PIM nor the STOPPFrail criteria showed any sort of correlation with frailty, while there was a weak and significant correlation with the LESS-CHRON criteria (28.6%, p=0.014). This may be due to the fact that the degree of frailty of the patient in our cohort did not exceed the threshold for which the STOPPFrail tool was designed.

At the same time, prognostic assessment[19] and Barthel index[18] again showed a weak but significant correlation with the LESS-CHRON criteria, but no correlation with the STOPPFrail tool. This could be explained by the fact that the LESS-CHRON criteria incorporate as part of the clinical evaluation of patients.

Consequently, one can deduce that the LESS-CHRON tool better adapts to the patient's clinical and prognostic context, including a greater number of criteria in older chronic

patients with multimorbidity. However, given the low correlation rates, it would be desirable to design new studies with a larger sample focused on this aspect.

Limitations

Among the limitations of the study, we highlight that the most recent version of STOPPFrail was not used. In addition, section A was removed from it in order to make a more realistic comparison between deprescribing criteria. Expanding this study to a larger number of patients would provide more reliable data on the correlation between the tools and the clinical parameters analyzed.

Conclusions and Implications

In summary, both tools have demonstrated a great capacity to identify PIM that can be deprescribed in an older polymedicated population with multimorbidity. In addition, they complement each other, covering a greater number of areas of pharmacotherapy between the two. Though, because STOPPFrail was designed and validated in a population with a poor prognosis and great frailty, LESS-CHRON appears to have greater detection potential in the subgroup of patients analyzed. It is necessary to confirm these results in the context of applying a real-life criteria application.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Figure 1. A) Prevalence* of PIM with the STOPPFrail tool. B) Prevalence* of PIM with the LESS-CHRON tool. The physiological systems to which the criteria belonged were identified with an alphanumeric code (Supplementary Material S1 and S2). Categories A1 and A2 of STOPPFrail were not assessed because they are appropriateness criteria.

*Prevalence (%) was calculated as the ratio between the number of potentially inappropriate medications (PIM) identified for each criterion versus the total number of individuals included (n=83).

Prevalence of PIM in patients with multimorbidity according to LESS-CHRON and STOPPFrail criteria

Abstract

Objective: LESS-CHRON and STOPPFrail are criterion-based deprescribing tools. This study aimed to identify the prevalence of potentially inappropriate medications (PIM) with these tools in an outpatient, polymedicated, older population with multimorbidity.

Design: Single-center cross-sectional observational study.

Setting and Participants: PIM and criteria subject to deprescribing identified by each tool were collected in patients who were being followed up on outpatient internal medicine consultation.

Methods: PIM were identified by STOPPFrail and LESS-CHRON criteria reviewing medical histories and pharmacological treatments of the patients in the electronic health card system. Sociodemographic, clinical and pharmacological variables were recorded. A correlation analysis between treatment tools and clinical values was performed using the non-parametric Spearman's Rho correlation.

Results: Eighty-three patients with a median of 14.4 (12;17) prescribed drugs were included. The total number of PIM identified with LESS-CHRON was 158 vs. 127 with STOPPFrail. Eight of the 27 criteria (29.6%) for LESS-CHRON and 15 of the 25 for STOPPFrail were found to be not applicable. A significant correlation was obtained for both tools with the number of prescribed drugs at the time of inclusion. The Profund, Barthel, and VGI-index only showed a significant correlation with LESS-CHRON.

Conclusion and Implications: Both tools have shown the capacity to identify PIM that can be deprescribed in the population studied. However, LESS-CHRON appears to have

a greater detection potential in the subgroup of patients analyzed. STOPPFrail brings a certain complementarity in other areas of therapy not covered by LESS-CHRON.

Introduction

Advances in social health status translate to an increase in life expectancy and therefore progressive population aging, leading to a greater prevalence of chronic diseases[1,2]. These results are in the interrelated concepts of chronic complex patients or patients with multimorbidity and frail patients[3,4].

Patients with multimorbidity are defined as those patients who suffer from two or more long-term conditions[5]. In our setting, this definition was agreed on in the Integrated Care Process for Patients with Multimorbidity (ICPPMM), establishing a series of clinical categories to define these patients[6] to homogeneously identify them. As a result, this population is characterized as complex, with high mortality, dependence, limited functionality, and vulnerability[7]. Furthermore, most of these patients are polymedicated[8].

Due to the complexity in managing treatment in these patients, specific strategies are necessary to optimize pharmacological therapy for these patients. These consist of interventions to improve appropriateness, generally of a multidisciplinary nature[9], which manage to reduce drug-related problems and optimize costs derived from health care[10].

Deprescribing has recently been included as a relevant strategy in this type of patient, with good results[11]. It is a process to review and evaluate long-term therapeutic plans in order to withdraw, substitute or reduce the dose of those drugs that, under certain clinical conditions, could be considered unnecessary or have an unfavorable benefit-risk ratio[12].

There are numerous strategies to carry out deprescribing. According to the systematic review conducted in 2019[13], the two most ideal explicit tools for application in clinical practice and identification of potentially inappropriate medications (PIM) in older patients are LESS-CHRON[14] and STOPPFrail[15].

Both are criterion-based tools developed by an expert panel, who reached a consensus on the deprescribing scenarios to be included according to bibliographic evidence. For their part, the LESS-CHRON[14] criteria were designed for patients with multimorbidity or those with similar characteristics and were based on four basic aspects: the indication for which the drug is prescribed, the condition that allows deprescribing, the health variables to monitor and the follow-up time during which different health variables must be monitored. On the other hand, STOPPFrail is specifically geared toward older frail patients. This tool also takes into account clinical conditions to perform deprescribing, although it does not specify out health variables or monitoring parameters[15].

Although the STOPPFrail tool appears to be the most appropriate to be used in outpatients with multimorbidity under certain clinical conditions[6], the truth is that there are currently no studies comparing both tools. Therefore, the aim of this study was to identify the prevalence of PIM in this group of patients and to compare the detection potential of LESS-CHRON criteria to those of STOPPFrail as screening tools in this population.

Materials and Methods

This project was carried out at a reference university hospital located in Spain. The design consisted of a unicentric cross-sectional observational study with recruitment taking place between October 2020-April 2021.

Participants

Patients who were being followed up on outpatient internal medicine consultation were included. The following were the inclusion and exclusion criteria:

Inclusion criteria

• Polymedicated (>5 active drugs) and ≥65 years patients who provided informed consent.

• Patients with multimorbidity or, in its absence, complex chronic patients[6].

• Patients who are undergoing treatment with at least one drug for the indication listed in one of the two tools being evaluated.

Exclusion criteria:

• Patients with unstable active malignant neoplasm and disseminated metastasis.

• Patients with neurological or mental disability without a legal representative.

• Patients in a clinical state of agony.

Procedure and study variables

Medical histories and pharmacological treatments of the patients were recorded in the electronic health-card system. PIM were identified by STOPPFrail and LESS-CHRON criteria. The LESS-CHRON tool includes 27 deprescribing criteria, considering the pairing indication-clinical situation offering the opportunity for deprescribing to be a criterion (Supplementary material S1). On the other hand, although the STOPPFrail tool is also based on 27 criteria (Supplementary material S2), two of them focus do not specify drugs with concrete withdrawal proposals, that is, they are not explicit criteria (Section A)[16]. Therefore, taking this into account, the above, a modified version of STOPPFrail was used to compare drug lists with specific indications. Each criterion of the tools allows to identify one or more PIM. The circuit that was carried out is shown in Supplementary material S3.

To respond to the objectives of the study, the following variables were recorded:

- Sociodemographic.
- Clinical:
  - Categories that identify patients with multimorbidity (Supplementary material S43)
  - Main comorbidities
  - Cognitive decline (Pfeiffer index)[17]
  - Functional decline (Barthel index)[18]
  - Prognostic stratification (Profund index)[19]
  - Frailty (Frail-VIG index)[20]
- Pharmacological:
  - Number of prescribed drugs at the time of inclusion.
  - Number of PIM detected.
  - Number of deprescribing criteria applicable.
  - Main active agent or pharmacological group to which each of the PIM belongs.

Analysis

Data description was carried out using frequencies for qualitative variables and median and IQR for quantitative variables because they were not distributed following a Normal distribution. The correlation between deprescribing criteria, pharmacological treatment and clinical variables was evaluated using the non-parametric Spearman's Rho correlation. All of the analyses were carried out using the statistical software Jamovi version 1.6.23.

To achieve a correlation coefficient other than 0 and an r of at least 0.30, assuming a type I error of 0.05 and a type II error of 0.20, it was necessary to include at least 80 subjects in the study[21].

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of XXX. Informed consent was obtained from all subjects involved in the study.

Results

Of all the patients who agreed to participate in the study, 83 patients met all inclusion criteria and then were included in the study. However, certain clinical variables were not recorded in some patients as reflected in Table I.

Demographic, pharmacological, and clinical characteristics

Of the patients analyzed, 81.5% did not show cognitive decline according to the Pfeiffer questionnaire. Similarly, the median of Barthel index showed slight dependence, ranging from 60 to 95 points, in 52.4% of the patients. In addition, the median obtained with the Profund index suggested a low-intermediate risk (21.5-31.5%) of death at one year after hospital discharge in 33.7% of the patients and an intermediate-high risk (45-50%) in 25.3%. The patient cohort showed mild frailty, but near the upper limit (mild frailty 0.2-0.36 and moderate frailty 0.39-0.53).

Based on established inclusion criteria, the population studied had a high prevalence of chronic disease. Thus, the median number of clinical categories presented was 3 (3;4). The most frequent clinical categories were heart failure (63.9%), chronic kidney disease (55.4%), anemia from gastrointestinal loss (48.2%), chronic respiratory disease (39.8%),

and ischemic heart disease (30.1%), respectively. With regard to the comorbidities recorded, the most common were arterial hypertension (88%), dyslipidemia (60.2%), atrial fibrillation (48.2%), and diabetes mellitus without complications (45.8%).

Assessment deprescribing with the LESS-CHRON and STOPPFrail tools

Regarding pharmacological treatment, as has already been commented, the median number of prescribed drugs per patient was 14.4 (12;17). The total number of PIM and deprescribing criteria identified with both tools are shown in Table 2. No significant differences were detected between the tools.

Of the cohort studied, 10.8% of patients (n=9) did not meet any deprescribing criteria for the LESS-CHRON tool and 13.3% (n=11) did not for the STOPPFrail tool.

The prevalence of PIM according to deprescribing criteria of each tool is presented in Figure 1.

In LESS-CHRON, 8 of the 27 criteria (29.6%) were found not to be applicable to any patient. The most prevalent criterion was withdrawal from benzodiazepine for insomnia (F3), with a value of 31%, followed closely by the deprescribing of antidepressants (F4) in the case of reactive depression (27%). In the case of STOPPFrail, 15 of the 25 criteria (60%) were not used and the withdrawal criterion of the lipid-lowering therapy (B1) was the most theoretically applied, present in 69% of patients.

Correlation analysis between pharmacological and clinical variables in both tools

A weak correlation between both tools was observed (29.5%, p=0.007 with respect to the criteria; 29%, p=0.008 with respect to the PIM for deprescribing) (Table 3A). As far as the correlation between the prescribed drugs in the population at the time of inclusion,

177 although there is a correlation in both tools, this was found to be greater in LESS-
178 CHRON.

179 Table 3B shows that none of the clinical indexes correlated with the STOPPFrail tool.
180 However, the Profund, Barthel, and frailty indexes did show a significant correlation with
181 LESS-CHRON for both the criteria variable and PIM for deprescribing.

182 **Discussion**

183 *Population target*

184 This study, which is the first to compare LESS-CHRON and STOPPFrail tools, confirms
185 that both explicit tools can be used to detect PIM in frail patients or those with a limited
186 life expectancy[13]. This is based on the fact that 77% of patients (n=64) met a minimum
187 of one deprescribing criterion in both tools. These results are consistent with the literature
188 and show the usefulness of deprescription tools in supporting the process[16, 22]. However,
189 the LESS-CHRON tool was found to have greater detection potential due to a higher
190 number of PIM obtained, and the correlation of the tool with pharmacological and clinical
191 parameters.

192 The differences found could be due to the target population towards which both tools are
193 directed. In this sense, the STOPPFrail authors geared the tool towards frail patients with
194 a life expectancy less than one year[15]. However, LESS-CHRON was designed to be
195 applied in chronic patients with multimorbidity or those with complex health needs[14],
196 which does not necessarily imply a short survival prognosis. In fact, survival prognosis is
197 included in this tool as a variable to consider in different proposed deprescribing criteria.

198 The cohort analyzed in this study is older, with a high degree of polymedication and
199 comorbidities. However, in terms of prognosis, the Profund index obtained implies a low-

intermediate risk of mortality at 12 months and Frail-VIG index indicates that elevated mortality at 1 year cannot be presumed[19, 20].

Theoretical applicability of the tools

Taking into account the theoretical applicability of the tools, combined to the fact that STOPPFrail[15] incorporates laxer withdrawal criteria, it could be expected that the number of PIM detected with this tool is greater than with LESS-CHRON. However, the results obtained show the opposite. This could be the consequence of a greater suitability of the LESS-CHRON criteria for this population or the tool having a greater sensitivity for the type of the prescribed medication in these patients. In this way, although the criteria of the STOPPFrail tool are more flexible, if the patient is not clearly at the end of their life, the application may be somewhat complex. This, together with the elimination of section A, could determine the lower detection capacity of PIM compared to previous studies of this tool[23].

Differences according to the functional system

In line with the criteria for each tool according to the drug involved, the differences according to the functional system can be analyzed. Consequently, the most notable is found in the systems or groups of drugs that are only represented in one of the tools. Specifically, in the case of STOPPFrail, the criteria related to the gastrointestinal tract (PPI and H2 antagonists), which make up 21% of the total, and in the case of LESS-CHRON, the group of benzodiazepines, Z drugs, and antidepressants (46% of the total), together with the scenario that suggests the deprescribing of allopurinol in the secondary prevention of gout (11%). In fact, they can be considered the criteria with greatest complementarity between both tools, representing a high percentage of the total criteria identified (40.8%).

Similarities between LESS-CHRON and STOPPFrail

First of all, it is important to mention that both tools are available in the scientific literature without any associated costs.

Regarding the similarities identified ~~between both tools~~, it is striking that they share 10 of the same criteria, although they slightly differ with respect to the clinical situation that allows for deprescribing. If the criterion referring to lipid-lowering therapies is specifically analyzed, it is the most applied in STOPPFrail (46% of the total), this figure is not maintained for LESS-CHRON since this tool establishes more restrictive conditions. The same is true for the third most prevalent criterion in STOPPFrail, where general withdrawal of calcium supplements is advocated, while LESS-CHRON specifies that patients must have a Barthel index <60 and be unable to walk, again creating differences in applicability (20% vs. 7%). In the opposite situation, the criterion indicating the deprescribing of alpha-blockers in prostatic hypertrophy is highly prevalent in LESS-CHRON, while in STOPPFrail, withdrawal was only recommended when the patient was catheterized. Finally, in the endocrine system, both tools indicate the withdrawal of oral antidiabetics, but due to differences in clinical conditions, the prevalence in LESS-CHRON is 14% vs. 8% in STOPPFrail.

Another relevant finding is that although the number of criteria analyzed for each tool was similar (27 in LESS-CHRON and 25 in STOPPFrail), it is true that in STOPPFrail only two criteria made up 65% of the total (criteria B1 and E1) and one of them affected 70% of the patients (criterion B1). However, in LESS-CHRON, the application of the different items was more homogeneous, distributed over a greater number of different criteria, and the sum of the three most applied criteria was less than 50% of the total.

It should be note that while this study was conducted, a new version of the STOPPFrail tool was published[24], which incorporates new criteria and eliminates others that had become obsolete. Nevertheless, none of the previously mentioned criteria that carried considerable weight in LESS-CHRON have been added in the new version.

Finally, it is important to mention that both tools consider criteria did not detect any candidate drug to be withdrawn, with a higher number in STOPPFrail compared to LESS-CHRON (15 vs 8 criteria). However, after the update to the English version of STOPPFrail[17], 6 of those 15 criteria have been eliminated, while 2 of them have been modified. With respect to LESS-CHRON, a study is currently underway to validate the criteria in a cohort of institutionalized patients and outpatients. With this study, data on usability and clinical utility will be obtained that will allow the criteria to be adapted to actual use needs.

In assessing the correlation between the clinical parameters, it is worth noting that neither the number of PIM nor the STOPPFrail criteria showed any sort of correlation with frailty, while there was a weak and significant correlation with the LESS-CHRON criteria (28.6%, p=0.014). This may be due to the fact that the degree of frailty of the patient in our cohort did not exceed the threshold for which the STOPPFrail tool was designed.

At the same time, prognostic assessment[19] and Barthel index[18] again showed a weak but significant correlation with the LESS-CHRON criteria, but no correlation with the STOPPFrail tool. This could be explained by the fact that the LESS-CHRON criteria incorporate as part of the clinical evaluation of patients.

Consequently, one can deduce that the LESS-CHRON tool better adapts to the patient's clinical and prognostic context, including a greater number of criteria in older chronic

patients with multimorbidity. However, given the low correlation rates, it would be desirable to design new studies with a larger sample focused on this aspect.

Limitations

Among the limitations of the study, we highlight that the most recent version of STOPPFrail was not used. In addition, section A was removed from it in order to make a more realistic comparison between deprescribing criteria. Expanding this study to a larger number of patients would provide more reliable data on the correlation between the tools and the clinical parameters analyzed.

Conclusions and Implications

In summary, both tools have demonstrated a great capacity to identify PIM that can be deprescribed in an older polymedicated population with multimorbidity. In addition, they complement each other, covering a greater number of areas of pharmacotherapy between the two. Though, because STOPPFrail was designed and validated in a population with a poor prognosis and great frailty, LESS-CHRON appears to have greater detection potential in the subgroup of patients analyzed. It is necessary to confirm these results in the context of applying a real-life criteria application.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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*Prevalence (%) was calculated as the ratio between the number of potentially inappropriate medications (PIM) identified for each criterion versus the total number of individuals included (n=83).

Table 1. Baseline characteristics of included patients

Characteristics	Patients (N=83)
Females, n (%)	38 (45.8)
Age, median (IQR)	80.5 (75.2; 85.3)
Clinical categories of PMM, median (IQR)	3 (3; 4)
Number of drugs per patient, median (IQR)	14.4 (12; 17)
Barthel index, n (%)* Median (IQR)	82 (98.8) 85 (56.3; 90)
Profund index, n (%)* Median (IQR)	83 (100) 6 (3; 9)
Pfeiffer questionnaire, n (%)* Median (IQR)	81 (97.6) 0 (0; 2)
Frail-VGI index, n (%)* Median (IQR)	74 (89.2) 0.36 (0.28; 0.47)

* n indicates the number of patients of the total included from whom the value of the specific index could be obtained.

Table 2. Comparison of the performance of LESS-CHRON to that of STOPPFrail criteria

Characteristics (n=83)	LESS-CHRON	STOPPFrail	P value
PIM identified *Total* *Median per patient (IQR)*	 158 2 (1; 3)	 127 1 (1; 2)	 0.069
Deprescribing criteria identified *Total* *Median per patient (IQR)*	 149 2 (1; 2.5)	 123 1 (1; 2)	 0.085
Patients without any deprescribing criteria	9 (10.8)	11 (13.3)	0.811

Table 3.

A. Correlation between deprescribing tools and prescribed drugs in patients included in the study

	No. of drugs prescribed	PIMs identified with STOPPFrail	STOPPFrail criteria applicable	PIMs identified with LESS-CHRON	
PIM identified with STOPPFrail	0.366		-		Spearman's Rho
	<0.001		-		p-value
STOPPFrail criteria applicable	0.359	0.997			Spearman's Rho
	<0.001	<0.001			p-value
PIM identified with LESS-CHRON	0.438	0.290	0.292	-	Spearman's Rho
	<0.001	0.008	0.007	-	p-value
LESS-CHRON criteria applicable	0.430	0.295	0.295	0.985	Spearman's Rho
	<0.001	0.007	0.007	<0.001	p-value

B. Correlation between clinical variables and deprescribing tools

	PIMs identified with STOPPFrail	STOPPFrail criteria applicable	PIMs identified with LESS-CHRON	LESS-CHRON criteria applicable	
Frail-VGI index	0.010	0.025	0.241	0.286	Spearman's Rho
	0.935	0.834	0.039	0.014	p-value
Barthel index	-0.071	-0.121	-0.241	-0.277	Spearman's Rho
	0.535	0.277	0.029	0.012	p-value
PROFUND index	-0.029	0.003	0.247	0.278	Spearman's Rho
	0.798	0.976	0.024	0.011	p-value
Pfeiffer questionnaire	0.106	0.029	-0.048	-0.026	Spearman's Rho
	0.346	0.795	0.672	0.818	p-value

Figure

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