PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of FORTA, PRISCUS and EU(7)-PIM list on identifying potentially inappropriate medication and its impact on cognitive function in multimorbid elderly German people in primary care: a multicentre observational study
AUTHORS	Krüger, Caroline; Schäfer, Ingmar; van den Bussche, Hendrik; Bickel, Horst; Dreischulte, Tobias; Fuchs, Angela; König, Hans-Helmut; Maier, Wolfgang; Mergenthal, Karola; Riedel-Heller, Steffi; Schön, Gerhard; Weyerer, Siegfried; Wiese, Birgitt; von Renteln-Kruse, Wolfgang; Langebrake, Claudia; Scherer, Martin

VERSION 1 – REVIEW

REVIEWER	Fadare, Joseph Ekiti State University, Pharmacology and Therapeutics
REVIEW RETURNED	18-Apr-2021

GENERAL COMMENTS	Lines 63-64: Using median as a measure of central tendency may better represent the data Lines 131-135: Please write in prose form without the roman numbers Line 217: Please change table 1 to Table 1. Same to be done throughout the manuscript Lines 239-241: Mean <SD may mean that another measure of central tendency i.e. median may be more appropriate Line 255: It may not be appropriate to start off a statement with numbers. Kindly revise Lines 267-268: This statement should come under "discussion" Line 310: Kindly revise this statement for clarity Line 347: Please change to “Risk factors for potentially inappropriate medication use” The “limitations” to be summarized Also, the “conclusion” to be summarized Table 1: “total number [%] of drugs used” – Capitalize t – Total Same goes for “patients” in the table Table 3: Please capitalize the first letter of the headings – numbers – Numbers; male – Male etc Tables 4 – 8; Same comments as above

REVIEWER	Bradley, Marie Food and Drug Administration Office of Global Regulatory Operations and Policy, Office of surveillance and Epidemiology, Divison of epidemiology
REVIEW RETURNED	19-Apr-2021

GENERAL COMMENTS	This was a cross sectional study that aimed to assess the frequency of potentially inappropriate medication (PIM) use (according to three PIM tools) and to examine the association between PIM use and cognitive function using data from the MultiCare cohort study in Germany. This study included OTC drugs in the evaluation of PIM which many previous studies on PIM have failed to account for and compared three distinct tools designed to assess PIM. However, I have some concerns which are outlined below. A rather significant concern is that many of the PIM tools include criteria which require information on the dose and frequency of drug use which was not collected in this study. This may explain the high PIM prevalence observed. Title and discussion 1.The term “inadequate” is used in the title and discussion/conclusion but then the term inappropriate is used throughout the text- consider replacing with inappropriate as this is a widely recognized term. Introduction 1.I would like to see more information on the rationale for examining PIM according to 3 different tools rather than selecting only one. A mention of the heterogeneity between the tools that is mentioned in the discussion may be well placed here. 2.If there have been previous studies on PIM in Germany please cite. If not this should be highlighted. 3. In the introduction you refer to three PIM tools but in the objective you state PIM lists consider using on term consistently throughout. Methods 1.Why was response from the MultiCare study so poor -46.2%? Is there information on those who did not respond? Is the sample generalizable? 2.How were general practices selected originally? 3.Please mention in methods that brown bag medication review was conducted in patients’ home. 4.The German Priscus list seems a little out of date- consider mentioning this. 5.In FORTA did you only identify C and D drugs? This needs to be made explicit in the methods. Results 1.I would like to see a table 1 with patient characteristics such as: mean age of patients, age categories sex, levels of comorbidity and polypharmacy education and income at baseline and any other relevant clinical or demographic information. 2.On line 257 please state the exact EU PIM criterion (Ibuprofen (>3×400 mg/d or for a period longer than one week) rather than just stating the drug name and similarly for any other criterion that consider dose and duration. 3.The PIM prevalence of 55% for FORTA and 70% for EU PIM are quite high- what are the explanations for this? Why were they so different to PRISCUS? Is it because it considers a narrower range

	of PIMs. I think a discussion of these differences would be interesting and useful to the readers Discussion 1.Statement of principal findings does not mention frequency of PIM- please revise in respect of the stated objectives. 2.It is stated “In general, our data are in good accordance with recently published data. Other studies detected EU(7)-PIM with a prevalence of 57.2% up to 72.8%. 1,24,25”- The citations used to support this comment refer to studies in other European countries for example Lithuania and Belgium- are these comparable to Germany? Also, it seems citation 25 used the STOPP START tool and not EU PIM List and is rather out of date (2008-2009) PIM may increase overtime? Have there been previous studies of PIM in Germany? 3.It is stated “Although all three lists were developed for the German or European drug market, there is – besides some classic drugs – a broad heterogeneity in detected PIM”……. I think this point is critical and should be mentioned in the introduction to justify the use of 3 different tools. However, I am not sure the subsequent sentience in the discussion addresses the issue “ “But Motter et al. explained that medication management in elderly multimorbid patients is highly complex because of limited data and that detecting potentially inappropriate medication and showing alternatives is an important step to improve medication safety in multimorbid elderly patients” In my opinion this doesn’t explain why there are so many different tools that make a complex process even more complex- consider revising. 4.In regards to why the FORTA list explains the relationship with cognitive decline better it is stated “A possible explanation is that FORTA list – in contrast to PRISCUS and EU(7)-PIM list – rates drugs indication-based”- Please expand on this as it is not clear why rating drugs by indication would better explain the relationship with Cognitive decline. 5.The authors state in the discussion that they did not collect information on dose and did not differentiate PRN and daily medications. This is a big limitation and needs to be mentioned in the methods section. Currently on line 143 in the methods it is stated “ and partly dosage and frequency – was performed” – is this correct? The reason as to why this was not available or collected should be included. Did this only apply to OTC drugs or all drugs- why didn’t you get this info from the GP surgeries? 6.As a result of the lack of dose info it was not possible to categorise PIM for PRISCUS and EU(7)-PIM list according to their dosing. How many criterion did the lack of dosing/duration apply to? Consider re-doing this analysis by excluding these criterion as a sensitivity analysis. There needs to be careful consideration on which tools can be used to asses PIM based on the data available. If you do not have the required information you cannot apply certain tools, or you need to restrict to certain criteria within

	the tool. It seems you have modified some of the criterion and that needs to be acknowledged. The results need to be re-interpreted in the face of these limitations as this is likely the reason for the high prevalence seen in this study. Conclusion 1.Conclusion is too long- please shorten 2.Conclusion states: “The broad heterogeneity of detected PIM with the different tools also reflects that we still need to improve the already existing PIM lists.” I would like to see more discussion of this topic in the discussion as your findings highlight this important point very well.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr. Joseph Fadare
Institution: Ekiti State University
Please state any competing interests or state ‘None declared’: none

1) ¬ Thank you for this advice. In the main text we presented both (median and mean) in order to exactly and precisely characterise the data. For the abstract we decided to only include mean and standard deviation.

2) ¬ Thank you for the comment we deleted the roman numbers (line 143 – 146)

3) ¬ Thank you for the advice. We corrected this in the manuscript.

4) ¬ Thank you for this advice. As written in the comment above (number 1), we reported median, mean and standard deviation. All data are presented in Table 2.

5) ¬ Thank you for this advice. We rewrote this sentence (line 266).

6¬ Thank you for this comment. During reviewing we decided to delete this sentence.

7) ¬ Thank you for this advice. Please see the corrected sentence in the manuscript (line 320 – 321).

8 ¬ Thank you for this advice. We corrected this (line 361).

9) ¬ Thank you for the advice. Please see the changes in the text (line 403 ff).

10) ¬ Thank you for this comment. We shortened the conclusion (line 439 - 456)

11) ¬ Thank you for this advice. We changed this.

12) ¬ Thank you for this advice. We changed this.

13) ¬ Thank you for this advice. We changed this.

14) ¬ Thank you for this advice. We changed this. In order to enhance the readability and the understanding we merged table 3 to 5.

Reviewer: 2
Reviewer Name: Dr. Marie Bradley
Institution: Food and Drug Administration Office of Global Regulatory Operations and Policy, National Cancer Institute Division of Cancer Control and Population Sciences
Please state any competing interests or state 'None declared': none

Title and discussion
1 ¬ Thank you for this advice. You are totally right and we changed the title and we made some corrections in the discussion and conclusion.

Introduction
1. ¬ Thank you very much for this advice. We provided more information in the introduction, including the heterogeneity of the different lists (line 111 – 116).

2. ¬ Thank you for this advice. There are studies on PIM in Germany, some only provide health insurance data, not including OTC drugs. Other studies only provide a small cohort or they included a much younger patient collective. And the huge studies in community-dwelling populations only focus on the prevalence and they do not investigate the association between PIM use and cognitive function. In addition there is to the best of our knowledge no study identifying PIM with FORTA list (line 117 - 120).

3. ¬ Thank you for this advice. We decided on the term PIM lists.

Methods
1. ¬ Thank you for the comment. We estimated a positive response rate from 40% to 50%. 7,172 patients were contacted for informed consent thereof 2,505 refused to participate, 1,242 did not reply within 4 weeks, 81 agreed but the baseline interview was not possible within defined timeframe of 16 months and 27 patients had wrong contact address in the general practitioners practice software. 3,316 patients agreed to participate and thereof 128 patients were excluded retrospectively (death, dementia, participation in other studies) (line 147 - 153). You can find more detailed information in the study protocol (Schäfer et al.: "The German MultiCare-study: Patterns of multimorbidity in primary health care – protocol of a prospective cohort study"). Besides this, there were well selected inclusion criteria (mentioned in the method section) which allows the assumption that the sample is generalizable.

2. ¬ Thank you for this question. On the basis of existing lists with all general practices for each city in Germany, practices with an electronical practice software and with general practitioners not older than 60 years old were contacted. Each practice should contact 50 patients. In order to recruit at least 3050 patients 120 up to 150 general practices were contacted. The exact study design is explained in detail in the study protocol (Schäfer et al.: "The German MultiCare-study: Patterns of multimorbidity in primary health care – protocol of a prospective cohort study").

3. ¬ Thank you for the comment. We included this information (line 157).

4. ¬ Thank you for this comment. In the method section we mentioned that the PRISCUS list was updated in 2011 and at the moment an expert team from Germany is working on an update for the PRISCUS list. But as PRISCUS is still a very common PIM list in Germany and is often included in the electronical software systems of both pharmacies and general practices, that is why we think that it is important to include this PIM list in our study. In addition we wanted to compare a national PIM list with a European PIM list (line 111– 113).

5. ¬ Thank you for the comment. No we did not only identify C and D drugs. We screened the whole medication for FORTA A-D drugs. We will clarify this in the method section (line 196).

Results

1. ¬ Thank you for this idea. We inserted a table (table 1) with the missing data (line 244).

2. ¬ Thank you for this comment. We think it is not appropriate to write down the exact EU(7) PIM criteria because – as described in the methods section - we were not able to analyse the data dependent on the dose. If we wrote the exact criteria of the EU(7) PIM including dose and duration, but used the criterion without that information we believe, that would confuse the reader. Of course, we are aware that we kind of overestimate ibuprofen PIM, because a proportion of patients only takes ibuprofen on demand, as it is explained in the discussion section.

3. ¬ Thank you for this important comment. PRISCUS list only comprises 83 drugs. In contrast FORTA comprises 296 drugs and EU(7)-PIM list comprises 282 drugs. This is one reason why we wanted to compare these three list. Among others, we wanted to know if the still quite popular and widely used PRISCUS list detects PIM in comparison to two more up to date PIM lists. Although PRISCUS list comprises less drugs than EU(7) and FORTA we were able to detect an association of PIM use and cognitive decline with the help of all three lists. So one can assume, that PRISCUS list still comprises the most important and most common PIM. We will clarify this in the discussion (line 328 - 331)

Discussion

1. ¬ Thank you for this comment. You are right and we added a sentence about the frequency (line 307 - 308).

2. ¬ Thank you for this comment. We checked the citations. Unfortunately we linked the wrong citation from Wauters et al. We corrected this issue (see reference 25). The oldest mentioned citation is from 2015, that is why we think the citations are up to date and are comparable with our presented data.
¬ EU(7)-PIM list is still pretty new in Europe and in Germany. In contrast the PRISCUS list is a common and widely used PIM list in Germany. But as the EU(7)-PIM list was developed for the overall European drug market we think it is appropriate to compare our findings with other European countries. As mentioned and cited in the manuscript there are some studies of about PIM use in Germany. For example Wickop, B. et al. Potentially Inappropriate Medication Use in Multimorbid Elderly Inpatients: Differences Between the FORTA, PRISCUS and STOPP Ratings, Toepfer, S. et al. Potentially inappropriate medication in older participants of the Berlin Aging Study II (BASE-II) – Sex differences and associations with morbidity and medication use. But they did not use EU(7) PIM list for their analyses. The ESTHER cohort study (Muhlack, D. C. et al. The associations of geriatric syndromes and other patient characteristics with the current and future use of potentially inappropriate medications in a large cohort study) detected EU(7)-PIM with a prevalence of 37,4% and PRISCUS PIM with a prevalence of 13.7%. Both prevalences are smaller than ours. But they included a much younger patient collective (50 – 75

years old vs. 65 – 85 years old) than we did (lines 318-321).

3. Thank you very much for this comment. We highlighted the heterogeneity of PIM and the lacking consequences in the introduction and also in the discussion (lines 108 – 116 and 350 - 356) and we revised the mentioned part about the complex process of detecting PIM.

4. Thank you for this comment. We think that FORTA list as an implicit PIM list may better address the individual patient need than an explicit PIM list like PRISCUS or EU(7)-PIM list. We outlined this fact in the discussion (lines 393 – 398).

5. Thank you for this advice. The drug data are completely self-reported. Due to this fact, especially the use of medication like PPIs, hypnotics and NSAIDs are likely to be underestimated. In addition, FORTA list does not differentiate between medication on demand and daily/regular medication. Because of the reasons above and in order to guarantee comparability we decided to include medication on demand into our analysis (lines 193 – 196).
 Data about, daily use or medication on demand were collected. The data about dosage was not collected sufficiently, so unfortunately we could not use the available data for the analysis (lines 155 – 159).
 We decided to conduct a sensitivity analysis, excluding medication on demand for EU(7)-PIM (14.5% medication on demand) and PRISCUS list (16.2% medication on demand). We could confirm that there is still a significant association on the cognitive function between PRISCUS/EU(7)-PIM list without medication on demand (line 410 – 424).

6. Thank you for this important comment. PRISCUS and EU(7)-PIM list provided for a lot of drugs only the recommendation “reduced initial doses” (“start slow”) or information about dose adjustment for patients with renal insufficiency are provided. Only for some drugs the PRISCUS and EU(7)-PIM lists provides information about the exact maximum daily dose. And also for a lot of drugs classified as “N” according to the ATC Code it is only stated: “Use the lowest possible dose, up to half of the usual dose”. So unfortunately, it is not uncommon that not all information are provided to analyse PIM dose-dependently in large studies. For example Mielke et al (“Self-reported medication in community-dwelling older adults in Germany: results from the Berlin Initiative Study“) identified dose-independent PRISCUS PIM with a prevalence of 15%. We might have detected higher prevalences of PIM use because of our well selected inclusion criteria’s. For example we only included patients with at least three chronic diseases. Most studies state a definition of two chronic diseases or include all patients 65 years old and older, irrespective on the number of morbidities. In addition another study only used health insurance data, that do not offer any information about dose and duration (Schubert et al: Prescribing potentially inappropriate medication (PIM) in Germany's elderly as indicated by the PRISCUS list. An analysis based on regional claims data”). Toepfer et al did not explain how exactly they classified the drugs according to PRISCUS and EU(7)-PIM list. And also the ESTHER cohort study did not provide data about dose and duration for the whole cohort (lines 405 – 409).

Conclusion

1. Thank you for this advice. Please see the new shorter version in the manuscript (lines 439 – 456).

2. Thank you for this important advice. We will highlight this point in the discussion (lines 351 - 356).

VERSION 2 – REVIEW

REVIEWER	Fadare, Joseph Ekiti State University, Pharmacology and Therapeutics
REVIEW RETURNED	02-Jul-2021

GENERAL COMMENTS	The use of mean instead of median under the results need to be addressed. Please see Lines 64-65, 260. Thank you

REVIEWER	Bradley, Marie Food and Drug Administration Office of Global Regulatory Operations and Policy, Office of surveillance and Epidemiology, Divison of epidemiology
REVIEW RETURNED	14-Jul-2021

GENERAL COMMENTS	Discussion There still needs to be a clear sentence outlining the problem with assuming use of, for example, omeprazole is inappropriate in the absence of come qualifier such as at certain doses or for certain durations The authors conducted a sensitivity analysis excluding PRN drugs from PRISCUS and EU-PIM and still found an association between PIM and cognitive decline but how did this exclusion affect prevlances of PIM? I think there still needs to be a comment on this that inclusion of PRN drugs may have over estimated the PIM prevalence. “By identifying PIM with FORTA, PRISCUS and EU(7)-PIM list and revealing that cognitive impairments is associated with PIM use, we are able to show the negative impact of PIM use on elderly patients outcome, underlining the importance to reduce the amount of PIM in elderly patients.” Care is advised with this sentence as you saw an association …… this is not evidence of causation and so you were not able to show a negative impact. Consider deleting this paragraph from the conclusion as it is not related to the findings of this study. “It is important to have tools to identify PIM in order to improve the medication safety. In addition, for in- and outpatient care it is important to know that appropriate and valid tools for identifying potentially inappropriate medication in elderly patients are existing. But the broad heterogeneity of detected PIM with the different tools also reflects that we still need to improve the already existing PIM lists. “ I suggest as suggested by the Editor that someone proficient in English needs to read and edit this paper before publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Name: Dr. Joseph Fadare

Institution: Ekiti State University

Please state any competing interests or state ‘None declared’: none

1) Thank you for this advice. We included that we used the mean for presenting our results (line 256).

Reviewer: 2

Name: Dr. Marie Bradley

Institution: Food and Drug Administration Office of Global Regulatory Operations and Policy, National Cancer Institute Division of Cancer Control and Population Sciences

Please state any competing interests or state ‘None declared’: none

Discussion

1) Thank you for this comment. We wrote a sentence outlining this problem (lines 407 – 409).

2) Thank you for this comment. You are right, we now address this fact in the strength and limitations section (lines 419 – 420).

Conclusion

1) Thank you for this comment. You are completely right and we changed the sentence (line 446 – 449).

2) Thank you for this advice. We shortened the paragraph, but we think that it is important to highlight the broad heterogeneity of the different PIM lists (line 449 – 452).