Reviewer’s report

Title: Impact of NPS MedicineWise general practitioner education programs and Choosing Wisely Australia recommendations on prescribing of proton pump inhibitors in Australia

Version: 1 Date: 06 Dec 2019

Reviewer: ILA HARRIS

Reviewer's report:

Thank you for this interesting study addressing the important issue of overprescribing of unnecessary and long term PPIs.

It is stated that the MedicineWise program's purpose was to reduce unnecessary prescribing of PPIs and that the objective of this study was to evaluate the impact on unnecessary prescribing. However, there were no diagnoses reported in this study to determine if the PPIs that were prescribed were necessary (e.g., Barrett's or ulcer) or unnecessary (dyspepsia, long term for GERD). This was noted as a limitation, which is good; however, the objective should be changed. In addition, if the outcome/objective was to evaluate overall PPI prescribing, than primarily the overall PPI prescribing/dispensing should be reported, along with the p value and significance, and the main conclusion should be about overall PPI prescribing. The current focus of the results/conclusions are on standard strength versus low strength dispensing. If this is the main result/conclusion, then the objective should be changed, and the background should be about PPI dose and not PPI use in general. I am not aware of studies that long-term PPI use at a "low" dose versus a "standard" dose has differences in long-term adverse effects. If the focus of the study is on using lower PPI doses, then please include any studies that evaluate/conclude that low strength/dose PPI have fewer adverse effects than standard strength/dose PPIs.

No information was provided about duration of PPI in individual patient to determine if it was appropriate or not (e.g., < 8 weeks for may be appropriate, but longer term is not for many indications). Is this information available? If so, please add it. If not, this should be a limitation. Some prescribers may appropriately prescribe PPIs for 4-8 weeks then no longer prescribe them. If they do this for all their patients with GERD, actual prescribing may not change, and it may not actually be inappropriate.

Page 3, Line 20-21: I would recommend adding that "long-term" use of PPIs is linked to adverse outcomes (not well documented for appropriate short term use of 8 weeks or less).

It is stated that the MedicineWise campaign also educated consumers. Only dispensing of PPIs was evaluated. It is possible that consumers/patients filled the prescriptions for the PPIs but didn't actually take them, or only took them on-demand or every other day. Add as a limitation that the outcome measure was PPI dispensing, and that if/how they actually took the med is unknown. If it is free they could still be filling it and not taking it or not taking it daily. In the US, we also have patients on auto-fill, where meds are automatically filled monthly (often
mailed or delivered regularly to the patient until someone actually discontinues the med). If that is a system in Australia as well, it should also be included as a limitation.

Please describe the national medicines dispensing records from the PBS that were used in the analysis of GP prescribing in more detail, especially for those readers outside of Australia.

It is stated that this summarizes medicines prescribed. Does this include medicines prescribed but then not picked up by the patient? Or do the records only include those dispensed and actually picked up by the patient? In the US, some of the prescribing records (such as the ones in our electronic health records) only record that the medicine was prescribed and "filled" by the pharmacy, and not actually picked up by the patient.

I recommend changing Table 2 to define only the exact doses/dose range for each PPI for standard and low dose/strength categories that were utilized for this study. Table 2 and the text surrounding PPI dosing/strengths is currently confusing. This study was done prior to May 2019. Which dosing scheme was used in the study? The text can say that the categories changed after completing the study/data analysis, but having it in the table confuses the reader. Also, prior to May 2019, there was no standard dose in the chart, but yet standard dose was mentioned in the study. The text states what was used for categorizing dosing of esomeprazole ("for simplicity") but this is different than what is in the table. Please clarify. The methods also discuss only standard and low strength/dose PPIs; however, Table 4 includes "high" and "highest" dose for the study period prior to 2019, and no "standard" dose.

Please be consistent with use of "dose" and "strength" and only use one of those terms throughout the text and tables. It is not clear if they meant to be interchangeable.

Page 5 lines 1-7 and Table 1 footnotes: This is confusing. Please clarify. Readers from countries out of Australia may not know what strengths are available OTC vs Rx, and if dosing is different in Australia, and what the "highest strength available" of the different PPIs is.

It would be helpful to have information on PPI indications and if these were all PPI prescriptions or only linked to inappropriate long-term prescriptions. Was this information collected and is it available?

Page 4, lines 5-9. Was diagnosis not included in the feedback to educate the GPs on if the prescriptions were appropriate or not? And, what time frame is this for the 6 or more prescriptions dispensed to define "long-term" treatment. And please define what it is for 1 prescription to be dispensed. Does this mean one 1 month supply? In the US, we often dispense 90 day supplies.

The results in the abstract and text are not clear about TOTAL dispensing of all strengths of PPIs because standard strength (decrease) and low strength (increase) mentioned separately for an earlier time frame, then it states "total" for June 2016. Is the total in June 2016 dispensing rates for ALL strengths of PPIs? Was the 8.6% total decrease in overall PPI dispensing significant and what was it compared to- prior to both educational interventions? This should be included. If the 8.6% overall decrease in PPI dispensing is not significant, cannot actually conclude that there
was a decrease in PPI prescribing after this intervention. This total should be stated first, as it is the most important thing (rather than the change in standard and low doses separately). Also, actual rates of total PPIs dispensed per 1000 prescribers before and after the interventions should be reported. Relative reduction in risk/prescribing often looks "better" than actual #s. This data was reported for specific strengths but not overall PPIs. Decreasing dose is okay, but the ultimate goal is getting patients off unnecessary PPIs.

Results section: The dispensing rate of low strength PPIs in the two time periods is not clear. Earlier, it is stated that the low strength dispensing rate increased in the earlier time period but not in the later. But in lines 52-54, it state that the earlier time period had an increase in low strength prescribing of 5.6% by March 2015 and an increase by June 2016 by 5%.

Table 4 needs more information in order to be helpful. What are the dates evaluated here? Which intervention/time period?

It would be helpful to have a fitted model for overall dispensing of all strengths of PPIs. Or at least more objective data/#s for overall PPI dispensing rates before and after the interventions.

Page7 Line 14-17: the wording is strong to say it is unlikely that patients switched to OTC medications ("unlikely" is used twice). Make the wording less strong. Although it is possible, it is purely assumption and cannot be proven. It should just be a limitation. The statement says that patients have limited funds so are unlikely to pay if they can get it cheaper or free if prescribed by their doctor. The doctor could have stopped prescribing it (or refused to prescribe it anymore) to follow the MedicineWise recommendations, which forced the patient to get it OTC.

Are the methods appropriate and well described? If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls? If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown? If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?
4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?
5. Do you have any other financial competing interests?
6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal