Author’s response to reviews

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

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ILA HARRIS (Reviewer 3): 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. The study background has been changed to reflect the aims of the study which was to look at stepping down from PPIs over time. This corresponds to the messages in the programs and follows guidelines. We cannot measure if treatment is appropriate or not so we are measuring the rate of prescribing of different strength PPIs.
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.

We are concerned about the cost to the government and the unnecessary exposure and cost to patients. Our content did not encourage stepping down treatment based on an assumption that low strength PPIs would have less long-term adverse events than higher strength. We acknowledged that these adverse events are rare and that there is not much in the published literature to justify the differences in these events based on strength. By encouraging stepping down, including stopping PPIs as outlined in the guidelines, we expected the outcomes would include less adverse events as well as cost to the government and the patients. We are not claiming that a lower strength will result in less adverse events but would improve quality use of medicine based on guidelines.

No information was provided about duration of PPI in individual patient to determine if it was appropriate or not (e.g., &lt; 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.

The data we have is based on the general practitioner not the patient. We cannot use the data we have to determine the duration of treatment for individuals. This has been added as a limitation. We have already stated in the limitations that we cannot determine if treatment was appropriate based on the data we have used.

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).

We would prefer not to say that long term use of PPIs is linked to adverse outcomes as the literature has shown that some adverse events can occur within the first few weeks of treatment (see reference 12).

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.

We have added more information in the limitation section about how we do not know if patients take medicines dispensed to them. Australia has no system of automatic refills through community pharmacies, although a reminder system can be set up with text messaging although this is not a universal system.
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. We have added an additional sentence on PBS data to explain that is an administrative dataset. 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.

The PBS data only included information about medicines provided to patients (or their carer) from a pharmacist. It is possible that a patient provides the prescription to the pharmacist and then leaves it behind. In this case the pharmacist has gone through the PBS recording system and it will be counted as dispensed even if the patient didn’t pick it up although there is no information about this available.

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. We have deleted table 2 and added strengths to Table 1 for ease of understanding. For the purposes of the study, we have categorised strengths as either standard or low. Table 4 is now Table 3 and we have changes the high to standard strength.

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. Dose and strength – we prefer to keep both dose and strength in the paper as they have different meanings. The strength of the medicines is the mg content whereas the dose is what the doctor prescribes, including the strength as well as the frequency of taking the medicine. They are not interchangeable. We have amended the last paragraph in the background to strength rather than dose.

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. We have deleted page 5 line 1-7 and left it as a footnote and the last paragraph in the background. We need this to be clarified but have not easier way of describing it.

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?
The PBS feedback data does not include diagnosis – we don’t know why the medicine is prescribed. This is a limitation of the intervention and we have added a sentence to the background description of intervention. We cannot capture indications for the PBS data set – this is outlined in the limitations.

Page 4, lines 5-9. Was diagnosis not included in the feedback to educate the GPs on if the prescriptions were appropriate or not?
The feedback does not include the reasons for prescribing PPIs and whether it was appropriate or not. A sentence has been added.
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 long term estimation of 6 prescriptions is equivalent to 6 months supply. A sentence has been added.

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.
The overall rate referred to standard strength and this has been made more explicit. We do not have the results overall and will not be able to calculate this now due to resource contraints.

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%.
We have modified the dates and made corrections.
Table 4 needs more information in order to be helpful. What are the dates evaluated here? Which intervention/time period?
Dates have been added to Table 3
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.
Not able to calculate this now due to resource contraints.

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.

unlikely is still used but we have refined this paragraph. Added that do not know if this is the case. Australian system is complex with the safety threshold and the PBS but we hope we have added enough information now given the word count restrictions. It is true that if a doctor refused to prescribe a PPI the patient could get OTC PPIs—have added this in. We have simplified the information about OTC medications.