PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in Acid Suppressant Drug Prescriptions in Primary Care in the United Kingdom: A Population Based Cross Sectional Study
AUTHORS	Abrahami, Devin; McDonald, Emily; Schnitzer, Mireille; Azoulay, Laurent

VERSION 1 – REVIEW

REVIEWER	Sander Veldhuyzen van Zanten Division of Gastroenterology University of Alberta Edmonton , Canada
REVIEW RETURNED	20-Jul-2020

GENERAL COMMENTS	The manuscript by four Canadian authors describes trends in prescribing of PPIs and H2-blockers over 30 years in the well-established Clinical Practice Primary Care database in the UK. This database is well established and collects prescriptions from a large number of general practitioners across the UK. It has been successfully used in many research publications. The data definitely are interesting, however, I think the manuscript can be improved, and I hope my comments are helpful in that regard. First, H2-blockers became available in the late 1970s and PPIs in the late 1980s. There is no doubt that PPIs are superior to H2-blockers, and that is the main explanation why they are much more commonly used. Given the timing of the drug development of these two classes of drugs it does not come as a surprise that there was a large increase in the use of proton pump inhibitors in the 1990s, that continued into the early 2000s. Concomitantly, H2-blocker use decreased, but interestingly enough, the total number of patients exposed to acid suppressive therapies, i.e. the summation of PPI users and H2-blocker users, was higher than either one alone, indicating increased use. All of this should be mentioned. Secondly, proton pump inhibitors became much cheaper once they came off patent, and this could have influenced increased use. The dates when PPIs and H2Rs came of patent in the UK need to be mentioned and analyzed. Different patent expiry dates may also influence use of individual PPIs relative to others. The manuscript needs to make some comments about these issues, especially in the discussion but likely also in the analysis. The price of medication, and when they came off patent, may certainly explain the overall use, especially among the PPIs. I do not know whether omeprazole is one of the cheapest generics in UK, but the figures provided make me wonder if this is the case. The other important issue is the accuracy of diagnostic classifications by GPs. As acid suppression works in GERD, peptic

	ulcer disease but also epigastric pain dominant dyspepsia (as opposed to upper abdominal bloating dominant dyspepsia), for a family physician it really does not matter all that much what the indication is. Data in the Western world have shown that GERD now is much more common than peptic ulcer disease and probably also than dyspepsia. Although I understand that the diagnoses are derived from the database, I think potential misclassification needs to be discussed in some detail in the discussion and possibly the Methods section. From my perspective, if a patient presents with indigestion, that is dyspepsia, reflux, or perhaps PUD it is perfectly reasonable to give this patient a trial of acid suppression. However, what this manuscript highlights, is that there a substantial proportion of patients in whom the indication, to continue the PPI long term, probably is not there. One way to further delve into this data might be looking at whether patients whose indication was strong (e.g. GERD) for the PPI prescription are more likely to stay on this medication long term than for example patients with dyspepsia. The other reason why I think the indications need to be taken with a certain level of uncertainty is the frequency of prescriptions for Barrett's esophagus. Certainly, in a population with 2 million people, the expectation is that more than 7,000 people would have a diagnosis of BE. Coming back to the indications for use, on Page 9, I think that a certain proportion of patients with stomach pain, gastritis or duodenitis, most likely fit the criteria at least for dyspepsia. I am interested to know whether use of baby aspirin is always captured in the database(s). For example in Canada, the country where I work, low dose aspirin is only available over the counter, and as such, not consistently captured in databases. This means that there might be uncertainty, in case of ASA in combination with anticoagulation or dial anti-platelet therapy, to give patients PPI prophylaxis. The other area that I have some comments about is the side effects, especially of PPI. The truth of the matter really is that PPIs have a very good safety profile. Although PPIs are associated with numerous diseases, for most of these, the evidence is not causal. True, well-established side effects of PPIs are increased risk of enteric infections, including C. Diff, microscopic colitis, interstitial nephritis and low magnesium levels. Osteoporosis and fractures has been largely debunked, as has dementia, pneumonia, and really to date there is no conclusive evidence that their use increases gastric cancer. This should be more clearly stated. In 18% of patients, no indication was recorded, but this reviewer does not agree that the authors simply accept that the use is off-label. This does probably not reflect the real world. In this group of patients is there corroborating evidence that PPIs are over prescribed? I assume the ratio of males to females in the extracted database was equal, and if so, this must be stated, so that females indeed are receiving the prescriptions more commonly. I think there are other data that also show that PPI use is higher in females. It is worth commenting on more. It would be interesting to break this down by the different indications, that were part of their database, to see if this is true across the board. In some ways, I thought it was too bad that the data were sliced in 30-day intervals. First, it would be interesting to know what the average duration of the first prescription is. In practice, it might be difficult for patients to be re-evaluated at exactly 4 weeks, and therefore prescriptions might be for a longer duration. Also, rather

	than looking at the total per person years of utilization, I would have liked to see a more broken down analysis of what proportion of patients received a prescription of duration 8 weeks in the first year, between 2 and 6 months, and 6-12 months. For example, a substantial proportion of patients with true reflux disease require long-term maintenance therapy. A good reference for this is the Montreal Classification paper, published in the American Journal of Gastroenterology. Certainly, for GERD there is good evidence, that on-demand use of PPIs work and this may be another explanation for why people use PPIs on a regular basis, but less than continuous. See for example, the publication by Zacny et al., APT 2005, https://doi.org/10.1111/j.1365-2036.2005.02490 As already mentioned, in the Results on Page 15, rather than reporting solely the peak intensity of number of prescriptions per thousand-person year's use, I would much prefer to see data on the annual proportion of individuals who received prescriptions and for what length of time. Looking at Figure 4, I raise the question whether the rate of persistent use of PPI at 37%, and 46% for H2-blockers, is more common in Barrett's esophagus, GERD and perhaps NSAID gastroprotection, than in dyspepsia or in the group of patients for whom there was no indication, or the indication was not evidence based. This would be interesting to report. Do I interpret the data correctly that 12.6% of PPI users were on continuous maintenance therapy for 5 years and 23% for H2 blockers? Given that the database goes back almost 30 years, I also would like to see data on longer-term use. In the Discussion, apart from mentioning the 10 million prescriptions that were given, I think the data will reveal more if it is expressed as the percentage of patients who received them. The NICE guidelines were only published in 2014. I am not sure the NICE guidelines led to a change in prescribing H2-blockers, unless the data from 2010-2015 show a different trend compared to 2015-2018 period. Overall, I do agree with the authors that there is likely over prescribing of PPIs and their data certainly would support that. In the references, there is some better summary data on safety and side effects of PPI. Several of the figures and Tables mention "Administrative Censoring". It would be good if this term is more explicitly explained and stated in the Methods section. In the Data Analysis section, the fonts used in various figures is too small.

REVIEWER	Tara Gomes / Teagan Rolf von den Baumen Unity Health Toronto, Canada / Leslie Dan Faculty of Pharmacy, University of Toronto, Canada
REVIEW RETURNED	22-Jul-2020

GENERAL COMMENTS	The authors report the findings of a population-based cross-sectional study using an administrative claims database in the UK. They describe patterns in proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) annual prescription rates and prescribing intensity over a 29-year period. The authors note that this study is the largest and most comprehensive study to date describing trends of acid suppressant drugs. While this topic and volume of data is of interest, I believe that this manuscript would benefit from further revision and consideration of the suggestions below:

	Major comments: 1. The guidelines that the authors cite in the “Indications for Use” section include hypersecretory conditions as an evidence-based indication for lifelong PPI therapy. However, the authors included Zollinger-Ellison syndrome (severe hypersecretory disease), but not other hypersecretory conditions under the evidence-based indications. Can the authors explain this discrepancy? 2. In the methods, the authors indicate that "If none of these variables were recorded, we used the mode of the prescription duration” in reference to prescription duration. Was this the overall mode for all prescriptions, the mode in a specific year, or for the prescriber who wrote the prescription? Related to this point, the authors adjusted prescription duration for those prescriptions with >90 day length into 30 day prescriptions, but didn’t do the same for shorter prescriptions. How common were prescriptions with <30 day duration and how would lack of adjustment of these prescriptions impact the analysis? Did average durations of prescriptions change over time in the UK in general? If so, could this inappropriately influence trends? 3. In the results, the authors state that PPIs and H2RAs were more commonly prescribed in females. Although in general the prevalence appears to be higher among females in Figure 2, these differences are quite small, and it doesn’t appear that any statistical tests were conducted to determine if this difference is meaningful. Applying statistical tests to other differences reported (i.e. % of PPI and H2RA users who had evidence-based indication for use, etc.) would help support the authors’ interpretation of results. 4. Figures 1&2: I am trying to compare the findings in these two figures and there seems to be a discrepancy. For example, in 2018 the overall prevalence was 14.2%, but in Figure 2, it appears that the prevalence in men and women was approximately 2%. How can this be? 5. The authors state in discussion paragraph 2: “… a significant portion likely represents overtreatment and failure to re-evaluate for ongoing necessity.” Given that authors have access to indication, it would strengthen the manuscript to stratify Kaplan-Meier curves by indication to help readers understand how well persistence patterns align with recommended durations of treatment. 6. The authors state that (discussion paragraph 7) it is possible trends are underestimated because data included is from general practitioners only and not hospitals or specialists. Given that GPs are more likely to be involved with long-term therapy, is it possible that the dataset may over-represent patients on long-term therapy, and under-represent those on short-term therapy (i.e. those acutely ill and discharged with short-term prescription from hospital). 7. In the introduction, the authors do not discuss the role (if any) of H2RAs in NICE guidelines, but in the discussion (paragraph 2) they mention “given that H2RA prescribing intensity has been increasing from 2010-2018, this may suggest a gradual shift in prescribing to favour H2Ras following the guidelines.” More background on role of H2RAs in the NICE guidelines would give this statement more context. Furthermore, given this statement, did the authors consider conducting a time-series analysis to measure whether changing guidance through NICE significant impacted these trends?

	Minor comments: 1. There are some grammatical errors/run-on sentences in the manuscript which could be revised for clarity and readability (i.e. Discussion paragraph 2: “While use of H2RAs may be associated with delirium and acute interstitial nephritis, they are generally well tolerated compared to PPIs, and are more commonly associated with mile adverse effects like headache and constipation, not the serious adverse effects associated with use of PPIs”). 2. Can the authors clarify whether the CPRD captures prescriptions written or dispensed, and add relevant limitations (i.e. if dispensed only, don’t know about patient adherence; if prescribed only, don’t know if patient filled prescription or adhered). 3. Results, paragraph 2: can the authors include the denominator for these percentages (ie number of people newly initiating an acid suppressant drug)? 4. Figure 4: I’d suggest presenting both drugs on the same curve in one figure to better allow for comparison. Removing symbols for censoring would also make the two lines easier to compare. 5. In Results paragraph 4, where Supplementary Figure 5 is discussed, the authors describe value per 1000 person years, where the Figure’s y-axis is displayed in %. Can the authors clarify which measure was used? 6. Results, Paragraph 5: The authors mention Supp Table 3 with the sensitivity analysis by varied definition of ongoing use, but don’t summarize the findings at all. Inclusion of how the results shifted with changing definition would be helpful. Also – there is an error in Supp Table 3, under “7 day grace period” where the row titled “Treatment gap >60 days” should read “Treatment gap >7 days”. 7. Results, paragraph 5, the authors state that “H2RA users were equally likely to discontinue use due to a treatment gap exceeding 30 days, administrative censoring, or because of a switch to a PPI.” It is easy for this to be misinterpreted as the reasons for discontinuation among H2RA users being similar to that of PPIs. I would suggest rephrasing (e.g. “In contrast, approximately one-third of H2RA users discontinued due to each of: treatment gaps exceeding 30 days, administrative censoring, or because of a switch to a PPI”). 8. In the discussion, a citation would support the statement that “a significant portion likely represents overtreatment and failure to re-evaluate for ongoing necessity”.

REVIEWER	Yasuhisa Sakata Saga University, Japan
REVIEW RETURNED	22-Jul-2020

GENERAL COMMENTS	This manuscript reported the trends of acid suppressant drugs over time in the UK. The authors found that prescribing intensity of H2RAs has increased over the last decade, while prescribing intensity of PPIs has plateaued in recent years. The findings are interesting, but I have some comments. My comments are as follows. 1. This study demonstrates that the prevalence of PPI use has increased with time. Has the incidence of GERD or other acid-related disorders, most common indications for PPIs, been

	increasing with time in the UK.? In addition, has prevalence of NSAIDs or antiplatelet drugs been increasing in the UK? 2. Authors described that H2RA prescribing intensity has been increasing from 2010 probably following the new guidelines. Does this suggest that there are many patients whose symptoms improved even with H2RA? 3. Do the new guidelines recommend a switch to H2RAs from PPIs if acid suppressant drugs are needed after the first treatment course of PPIs? 4. This study showed an increase in use of H2RAs among the paediatric population over the past decade. What could be the reason for this trend? I hope these comments will be helpful.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Sander Veldhuyzen van Zanten

Institution and Country

Division of Gastroenterology

University of Alberta

Edmonton , Canada

Please state any competing interests or state 'None declared':

none

Please leave your comments for the authors below

The manuscript by four Canadian authors describes trends in prescribing of PPIs and H2-blockers over 30 years in the well-established Clinical Practice Primary Care database in the UK. This database is well established and collects prescriptions from a large number of general practitioners across the UK. It has been successfully used in many research publications.

The data definitely are interesting, however, I think the manuscript can be improved, and I hope my comments are helpful in that regard.

We thank the reviewer for the positive feedback. We also appreciate the thoughtful comments and suggestions; these have been addressed in detail.

First, H2-blockers became available in the late 1970s and PPIs in the late 1980s. There is no doubt that PPIs are superior to H2-blockers, and that is the main explanation why they are much more commonly used. Given the timing of the drug development of these two classes of drugs it does not come as a surprise that there was a large increase in the use of proton pump inhibitors in the 1990s, that continued into the early 2000s. Concomitantly, H2-blocker use decreased, but interestingly enough, the total number of patients exposed to acid suppressive therapies, i.e. the summation of PPI users and H2-blocker users, was higher than either one alone, indicating increased use. All of this should be mentioned.

We agree with the reviewer that PPIs are superior to H2-blockers and we have described this in the introduction on page 5, paragraph 1:

"While both drug classes have been used for over three decades, PPIs have been shown to have superior efficacy in reducing stomach acid compared to H2RAs and are thus more favourably used."

We have also added a sentence to the introduction describing the market availability of each drug class on page 5, paragraph 1:

"The first H2RA, cimetidine, was approved for use in the United Kingdom (UK) in 1976, while omeprazole, a PPI, was later approved in 1989."

We also clarified the patterns of use in the discussion (Page 15, paragraphs 1 and 2):

"The overall prevalence of PPI prescribing has increased from 1990 to 2018, while the prevalence of H2RA remained low."

"While H2RAs are considerably less popular than PPIs, we observed almost 10 million prescriptions within our study period, suggesting that their use has not been completely supplanted by PPIs."

"…while the prevalence of acid suppressant drugs is consistent with the market availability of both drug classes…"

Secondly, proton pump inhibitors became much cheaper once they came off patent, and this could have influenced increased use. The dates when PPIs and H2Rs came of patent in the UK need to be mentioned and analyzed. Different patent expiry dates may also influence use of individual PPIs relative to others. The manuscript needs to make some comments about these issues, especially in the discussion but likely also in the analysis. The price of medication, and when they came off patent, may certainly explain the overall use, especially among the PPIs. I do not know whether omeprazole is one of the cheapest generics in UK, but the figures provided make me wonder if this is the case.

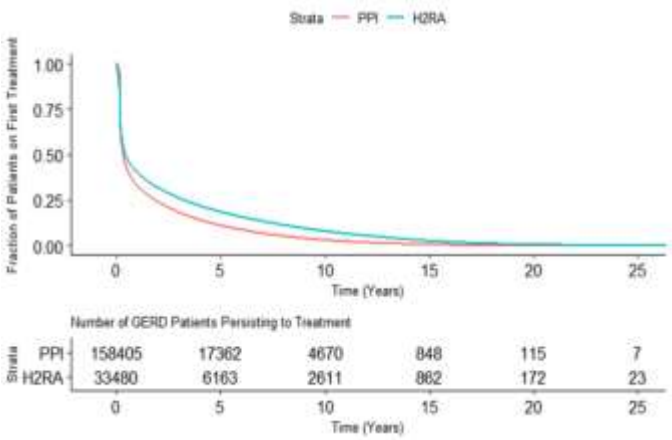
Unlike in Canada, universal health care in the UK includes a reduced cost of medications. All outpatient prescription drugs are subject to a copayment of GBP 8.80 per prescription. As a result, the price is unlikely to influence use, so we chose not to focus on cost in our analyses. An economic analysis is outside the scope of this paper.

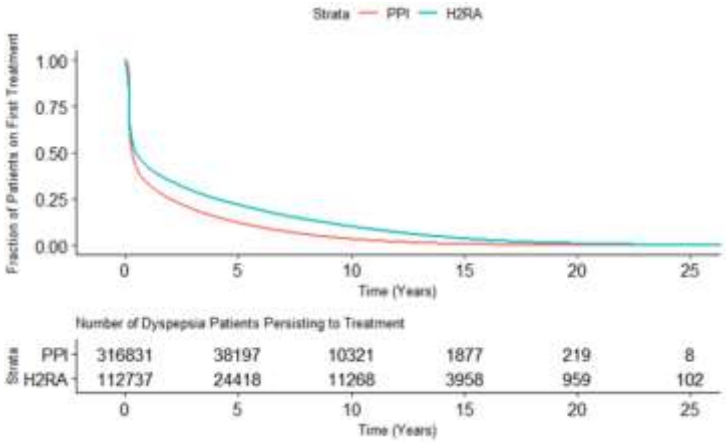
The other important issue is the accuracy of diagnostic classifications by GPs. As acid suppression works in GERD, peptic ulcer disease but also epigastric pain dominant dyspepsia (as opposed to upper abdominal bloating dominant dyspepsia), for a family physician it really does not matter all that much what the indication is. Data in the Western world have shown that GERD now is much more common than peptic ulcer disease and probably also than dyspepsia. Although I understand that the diagnoses are derived from the database, I think potential misclassification needs to be discussed in some detail in the discussion and possibly the Methods section.

As shown in Table 1, GERD is more common than peptic ulcer disease in our population. We would like to reiterate that the indications presented in the table are not mutually exclusive, so there is less potential for misclassification between indication categories, as an individual can be counted in multiple categories. Indeed, 31,591 PPI users and 9,299 H2RA users had a recorded diagnosis of both dyspepsia and GERD at the time of their first prescription, while 4,939 PPI users and 1,064 H2RA users had a recorded diagnosis of GERD and peptic ulcer disease.

From my perspective, if a patient presents with indigestion, that is dyspepsia, reflux, or perhaps PUD it is perfectly reasonable to give this patient a trial of acid suppression. However, what this manuscript highlights, is that there a substantial proportion of patients in whom the indication, to continue the PPI long term, probably is not there. One way to further delve into this data might be looking at whether patients whose indication was strong (e.g. GERD) for the PPI prescription are more likely to stay on this medication long term than for example patients with dyspepsia.

We thank the reviewer for highlighting this important point, which has better helped to clarify the persistence patterns in our population. As illustrated in the figures below, the persistence among patients with GERD (left) and those with dyspepsia (right) were relatively consistent.





Given that the indication categories are not mutually exclusive, there is some overlap between the patients contributing to persistence according to these granular indications. Thus, we elected to illustrate persistence patterns among the broader mutually exclusive indication categories (evidence-based, non-evidence based gastroprotection, off-label, and no recorded indication) in the manuscript (Supplementary Figures 7 to 10). These results are summarized on page 14, paragraph 2, and addressed in the discussion (Page 17, Paragraph 1):

"When examining persistence by indication, persistence to both PPIs and H2RAs was highest among patients with an off-label or no recorded indication for use (**Supplementary Figures 7** to **10**)".

"As illustrated by the stratified persistence patterns, a significant portion of this high persistence is among patients with an off-label, or no recorded indication for use. This provides further evidence on the inappropriate use of acid suppressant drugs."

The other reason why I think the indications need to be taken with a certain level of uncertainty is the frequency of prescriptions for Barrett's esophagus. Certainly, in a population with 2 million people, the expectation is that more than 7,000 people would have a diagnosis of BE.

We want to highlight that the indications reported in the manuscript were those recorded on or before the first prescription of a PPI or H2RA. Thus, it is possible that patients develop Barrett's oesophagus over the follow-up period. Moreover, Barrett's oesophagus is an extremely rare condition, which can be difficult to diagnose given that many individuals are asymptomatic (Runge et al., Gastroenterol Clin North Am, 2016). This may explain, at least in part, the low incidence of Barrett's oesophagus in this population.

Coming back to the indications for use, on Page 9, I think that a certain proportion of patients with stomach pain, gastritis or duodenitis, most likely fit the criteria at least for dyspepsia.

While we agree with the reviewer that it is possible that patients with stomach pain, gastritis or duodenitis may have dyspepsia, we based our indications categories according to recorded diagnoses in the CPRD only. As these patients had no diagnostic codes for dyspepsia at any time prior to their first prescription of an acid suppressant drug (or any other evidence-based indication), they were classified as off-label users if they had a recording of stomach pain, gastritis or duodenitis.

I am interested to know whether use of baby aspirin is always captured in the database(s). For example in Canada, the country where I work, low dose aspirin is only available over the counter, and as such, not consistently captured in databases. This means that there might be uncertainty, in case of ASA in combination with anticoagulation or dial anti-platelet therapy, to give patients PPI prophylaxis.

We thank the reviewer for raising this important point, which we have added to the discussion on page 18, paragraph 1:

“Lack of over the counter data may have led to the underestimation of patients using acid suppressant drugs for gastroprotection, as it is possible that some patients receive an NSAID prescription over the counter.”

The other area that I have some comments about is the side effects, especially of PPI. The truth of the matter really is that PPIs have a very good safety profile. Although PPIs are associated with numerous diseases, for most of these, the evidence is not causal. True, well-established side effects of PPIs are increased risk of enteric infections, including C. Diff, microscopic colitis, interstitial nephritis and low magnesium levels. Osteoporosis and fractures has been largely debunked, as has dementia, pneumonia, and really to date there is no conclusive evidence that their use increases gastric cancer. This should be more clearly stated.

We have reframed the introduction to include only these well-established risks (Page 5, paragraph 3), and provided a more balanced discussion of the potential associations with other adverse events in the discussion (Page 16, paragraph 3):

“These include enteric infections such as Clostridium difficile, acute interstitial nephritis, hypomagnesemia and increased intestinal colonization with multidrug resistant organisms.”

“This is particularly relevant as PPIs are associated with a number of serious adverse events including enteric infections and hypomagnesemia. While there is some evidence that use of PPIs may also be

associated with dementia, pneumonia and gastric cancer, not all studies have confirmed these associations."

In 18% of patients, no indication was recorded, but this reviewer does not agree that the authors simply accept that the use is off-label. This does probably not reflect the real world. In this group of patients is there corroborating evidence that PPIs are over prescribed?

We would like to reiterate how the indication categories were quantified. Patients were classified into indication categories a hierarchical manner as evidence-based (dyspepsia, gastroprotection, gastroesophageal reflux disease, peptic ulcer disease, Helicobacter pylori infection, Barrett's oesophagus, and Zollinger-Ellison syndrome), non-evidence based gastroprotection, off-label (stomach pain and gastritis or duodenitis) and no recorded indication. The patients who were classified as 'no recorded indication' had no diagnostic codes in their entire history for any of the evidence-based or off-label indications. This reflects what is currently known about PPI use, which suggests they are frequently prescribed to individuals without an indication for use. Thus, patients with no recorded indication are completely distinct from the patients with an off-label indication (stomach pain, gastritis or duodenitis). Finally, to prevent overcounting indications among individuals who are prescribed PPIs and H2RAs during follow-up, we recategorized indication categories according to the first of *either* a PPI or H2RA prescription. The new counts are illustrated in Table 1.

I assume the ratio of males to females in the extracted database was equal, and if so, this must be stated, so that females indeed are receiving the prescriptions more commonly. I think there are other data that also show that PPI use is higher in females. It is worth commenting on more. It would be interesting to break this down by the different indications, that were part of their database, to see if this is true across the board.

We thank the reviewer for pointing this out. We have added the proportion of females in the CPRD to the results Page 12, paragraph 1:

"Within a cohort of 14,242,329 patients (51.4% female) registered in the CPRD, 3,027,383 (21.3%) patients were prescribed at least one PPI or H2RA during the study period, corresponding to 58,926,373 and 9,386,908 prescriptions, respectively."

We have also added a supplementary table of indications stratified by sex, with results summarized on page 12, paragraph 2:

"When stratifying indications by sex, females were more commonly prescribed PPIs for off-label indications compared to males (Supplementary Table 3)."

In some ways, I thought it was too bad that the data were sliced in 30-day intervals. First, it would be interesting to know what the average duration of the first prescription is. In practice, it might be difficult for patients to be re-evaluated at exactly 4 weeks, and therefore prescriptions might be for a longer duration. Also, rather than looking at the total per person years of utilization, I would have liked to see a more broken down analysis of what proportion of patients received a prescription of duration 8 weeks in the first year, between 2 and 6 months, and 6-12 months. For example, a substantial proportion of patients with true reflux disease require long-term maintenance therapy. A good reference for this is the Montreal Classification paper, published in the American Journal of Gastroenterology. Certainly, for GERD there is good evidence, that on-demand use of PPIs work and this may be another explanation for why people use PPIs on a regular basis, but less than continuous. See for example, the publication by Zacny et al., APT 2005, https://doi.org/10.1111/j.1365-2036.2005.02490

We would like to clarify how prescribing intensity was calculated. We transformed longer prescriptions into 30-day equivalents so that we could calculate a consistent numerator for the intensity measure. This was done to prevent underestimating intensity, as the reviewer is correct in saying that it may be difficult for some patients to be re-evaluated every 4 weeks, and thus they might receive prescriptions of longer durations. Thus, one 90-day prescription is considered equivalent to three 30-day prescriptions for the intensity calculation. The length of the first treatment episode can be visualized clearly in the Kaplan-Meier curves, which show persistence to the original treatment course. In light of deprescribing initiatives and the new guidelines, persistence to a medication is more relevant than the length of a first prescription.

We agree with the reviewer that there are some patients for whom long term therapies are indicated. This is illustrated in the Kaplan-Meier curves which are stratified by indication in the supplementary materials (Figures 7 to 10). The proportion of patients persisting per year can be read off of these figures, with counts presented at 5-year intervals for ease of interpretation.

Finally, we agree with the reviewer that some patients may use acid suppressants irregularly. This is why we used a 30-day grace period to define continuous use. We changed the length of the grace period in a sensitivity analysis to determine the impact of imperfect prescription fillings or adherence within our population.

As already mentioned, in the Results on Page 15, rather than reporting solely the peak intensity of number of prescriptions per thousand-person year's use, I would much prefer to see data on the annual proportion of individuals who received prescriptions and for what length of time. Looking at Figure 4, I raise the question whether the rate of persistent use of PPI at 37%, and 46% for H2-blockers, is more common in Barrett's esophagus, GERD and perhaps NSAID gastroprotection, than in dyspepsia or in the group of patients for whom there was no indication, or the indication was not evidence based. This would be interesting to report.

We agree with the reviewer that persistence according to indications for use is an important addition to the manuscript, which has been described in detail above.

Do I interpret the data correctly that 12.6% of PPI users were on continuous maintenance therapy for 5 years and 23% for H2 blockers? Given that the database goes back almost 30 years, I also would like to see data on longer-term use.

The reviewer is correct in the interpretation of the persistence at 5 years. The complete picture of persistence over the study period is illustrated in figure 4, with the number of patients persisting to both treatments in 5-year intervals illustrated at the bottom of the figure.

In the Discussion, apart from mentioning the 10 million prescriptions that were given, I think the data will reveal more if it is expressed as the percentage of patients who received them.

While this is described extensively in the results, we have clarified the percentages of users in the discussion on page 15, paragraph 1:

"Throughout the study period, 21.3% of the CPRD population received at least one prescription for an acid suppressant drug (PPI only: 19.1%, H2RA only: 6%, PPI and H2RA: 3.8%)."

The NICE guidelines were only published in 2014. I am not sure the NICE guidelines led to a change in prescribing H2-blockers, unless the data from 2010-2015 show a different trend compared to 2015-2018 period.

We thank the reviewer for this point. When recalculating intensity in 5-year increments, we noticed a numerical error in the original version of the manuscript, which has now been corrected. For consistency, we now present all prescribing intensity results in 5-year increments, which can be found in Supplementary Table 4. Reclassifying intensity in shorter intervals allows us to examine the prescribing intensity around the time of guideline publication. This shows that the prescribing intensity of H2RAs plateaued in the five years prior to the guideline publication but increased by 5% per year in the four years following guideline publication. We have described these results in the results on Page 13, paragraph 2, and in the discussion on page 16, paragraph 1:

"PPI yearly prescribing intensity sharply increased during the first 5 years of the study period, moderately increased until 2004, after which prescribing intensity plateaued (Supplementary Table 4). In contrast, H2RA yearly prescribing intensity decreased from 1990 to 2009, and has begun to slightly increase over the past five years."

"Given that H2RA prescribing intensity has begun to increase following publication of the guidelines, this may suggest a gradual shift in prescribing to favour H2RAs."

Overall, I do agree with the authors that there is likely over prescribing of PPIs and their data certainly would support that. In the references, there is some better summary data on safety and side effects of PPI.

We agree with the reviewer that PPIs are frequently overprescribed. In light of this, we have provided a more balanced discussion on the safety of PPIs in the discussion, along with updated references (Page 16, paragraph 3):

"This is particularly relevant as PPIs are associated with a number of serious adverse events including enteric infections and hypomagnesemia. While there is some evidence that use of PPIs may also be associated with dementia, pneumonia and gastric cancer, not all studies have confirmed these risks."

Several of the figures and Tables mention "Administrative Censoring". It would be good if this term is more explicitly explained and stated in the Methods section.

We thank the reviewer for this suggestion and have described this term in the methods on page 10, paragraph 2.

"The end of a treatment episode was defined as the first of: 1) a treatment gap exceeding 30 days, 2) a switch from PPI to H2RA or vice versa, or 3) administrative censoring (i.e. if a practice stopped contributing data to the CPRD, a patient was no longer registered with their general practice, or if the study period ended)."

In the Data Analysis section, the fonts used in various figures is too small.

We have increased the font size in the figures.

Reviewer: 2

Reviewer Name

Tara Gomes / Teagan Rolf von den Baumen

Institution and Country

Unity Health Toronto, Canada / Leslie Dan Faculty of Pharmacy, University of Toronto, Canada

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

The authors report the findings of a population-based cross-sectional study using an administrative claims database in the UK. They describe patterns in proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) annual prescription rates and prescribing intensity over a 29-year period. The authors note that this study is the largest and most comprehensive study to date describing trends of acid suppressant drugs. While this topic and volume of data is of interest, I believe that this manuscript would benefit from further revision and consideration of the suggestions below:

We thank the reviewer for the overall positive comments on our manuscript. Please find our responses to your comments below.

Major comments:

1. The guidelines that the authors cite in the "Indications for Use" section include hypersecretory conditions as an evidence-based indication for lifelong PPI therapy. However, the authors included Zollinger-Ellison syndrome (severe hypersecretory disease), but not other hypersecretory conditions under the evidence-based indications. Can the authors explain this discrepancy?

We thank the reviewer for noting this discrepancy. According to the paper cited in the manuscript, Zollinger-Ellison syndrome is the only hypersecretory disease that would require continuous acid suppressant treatment. While other individuals who are 'hypersecretors' may be prescribed acid suppressants, this is determined according to basal acid outputs, which we do not have access to in the CPRD.

2. In the methods, the authors indicate that "If none of these variables were recorded, we used the mode of the prescription duration" in reference to prescription duration. Was this the overall mode for all prescriptions, the mode in a specific year, or for the prescriber who wrote the prescription? Related to this point, the authors adjusted prescription duration for those prescriptions with >90 day length into 30 day prescriptions, but didn't do the same for shorter prescriptions. How common were prescriptions with <30 day duration and how would lack of adjustment of these prescriptions impact the analysis? Did average durations of prescriptions change over time in the UK in general? If so, could this inappropriately influence trends?

We used the overall mode of all prescriptions for PPIs and H2RAs, separately, as this did not change over time. We want to clarify that we standardized prescriptions to 30-day intervals to calculate intensity. This means that three 30-day prescriptions were equivalent to one 90-day prescription. This was done so that intensity would not be inappropriately influenced by prescriptions of long durations. Given that 7-day prescriptions are only indicated for the management of H. pylori, these short duration prescriptions are not common (less than 2% of all prescriptions) and are unlikely to substantially influence the reported trends.

We clarified this in the methods section on page 8, paragraph 1:

"If none of these variables were recorded, we used the mode of the prescription duration for PPIs and H2RAs, separately."

3. In the results, the authors state that PPIs and H2RAs were more commonly prescribed in females. Although in general the prevalence appears to be higher among females in Figure 2, these differences are quite small, and it doesn't appear that any statistical tests were conducted to determine if this difference is meaningful. Applying statistical tests to other differences reported (i.e. % of PPI and H2RA users who had evidence-based indication for use, etc.) would help support the authors' interpretation of results.

We thank the reviewer for the suggestion. However, we would like to reiterate that this study does not aim to address hypothesis testing, as this is a descriptive cross-sectional study. Moreover, given that statistical tests depend on power, and this is a very large study, we would likely observe very significant findings for all differences. There is guidance against using statistical tests (and p-values) for differences in characteristics (Greenland et al, Eur J Epidemiol, 2016).

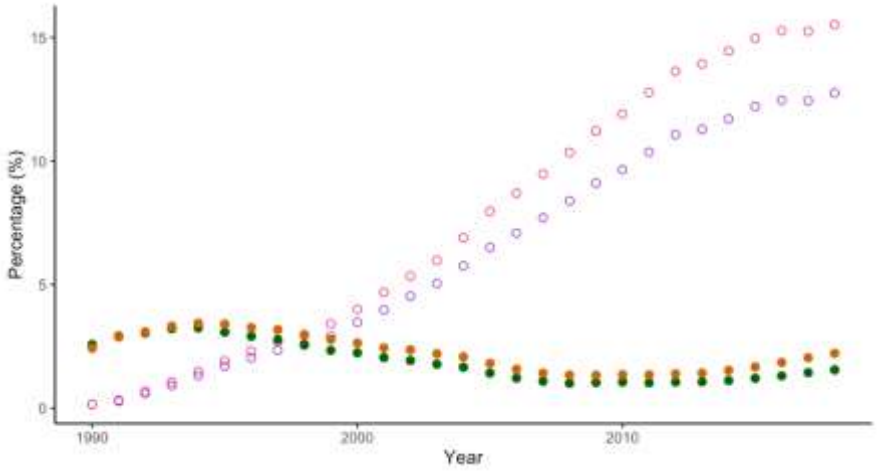
Nonetheless, to prevent overinterpreting the relatively small sex difference in prevalence of H2RAs, we now focus on the sex difference in PPI prescribing in the manuscript (Page 13, Paragraph 1, Page 16, paragraph 2):

"PPIs were more commonly prescribed in females and both drug classes were more commonly prescribed in adults at least 60 years old"

"Our study demonstrated a sex difference among PPI prescribing patterns and an age difference among prescribing patterns of both PPIs and H2RAs; women were more frequently prescribed PPIs and adults at least 60 years old were more frequently prescribed both drug classes. As women are more likely to report symptoms of gastric reflux than men,[24] this would lead to more frequent prescribing of acid suppressant drugs to manage these symptoms. Moreover, dyspepsia, the most common evidence-based indication, was more commonly diagnosed in women."

4. Figures 1&2: I am trying to compare the findings in these two figures and there seems to be a discrepancy. For example, in 2018 the overall prevalence was 14.2%, but in Figure 2, it appears that the prevalence in men and women was approximately 2%. How can this be?

We thank the reviewer for pointing out this important discrepancy. Figure 2 was incorrectly uploaded as Supplementary Figure 2, which shows the prevalence of use among new users. We have presented the corrected figure in the manuscript to show overall PPI and H2RA prevalence by sex.



5. The authors state in discussion paragraph 2: "… a significant portion likely represents overtreatment and failure to re-evaluate for ongoing necessity." Given that authors have access to indication, it would strengthen the manuscript to stratify Kaplan-Meier curves by indication to help readers understand how well persistence patterns align with recommended durations of treatment.

We thank the reviewer for this important suggestion. We have provided a full response to reviewer 1 above and have added Kaplan-Meier curves stratified by indication to further illustrate persistence patterns.

6. The authors state that (discussion paragraph 7) it is possible trends are underestimated because data included is from general practitioners only and not hospitals or specialists. Given that GPs are more likely to be involved with long-term therapy, is it possible that the dataset may over-represent patients on long-term therapy, and under-represent those on short-term therapy (i.e. those acutely ill and discharged with short-term prescription from hospital).

We thank the reviewer for highlighting this point. This has been added to the discussion as a limitation of the data (Page 18, Paragraph 1):

"However, it remains possible that the lack of hospitalization data led to the underestimation of patients requiring short-term treatment with acid suppressant drugs."

7. In the introduction, the authors do not discuss the role (if any) of H2RAs in NICE guidelines, but in the discussion (paragraph 2) they mention "given that H2RA prescribing intensity has been increasing from 2010-2018, this may suggest a gradual shift in prescribing to favour H2Ras following the guidelines." More background on role of H2RAs in the NICE guidelines would give this statement more context. Furthermore, given this statement, did the authors consider conducting a time-series analysis to measure whether changing guidance through NICE significant impacted these trends?

We have added a sentence to the introduction (Page 6, Paragraph 1) on the NICE recommendations for H2RA treatment:

"Treatment with H2RAs is recommended when patients are unresponsive to PPIs"

Given that PPI prescribing intensity has plateaued, while H2RA prescribing intensity has recently been increasing, this could be due, in part, to the most recent guidelines, which recommend shortest durations possible for PPI prescriptions. This has been described in the discussion on page 16, paragraph 1:

"To our knowledge, this is the first study to describe contemporary prescribing practices following the most recent NICE recommendations in 2014.[16] Given that H2RA prescribing intensity has begun to increase following publication of the guidelines, this may suggest a gradual shift in prescribing to favour H2RAs. Indeed, the guidelines recommend treatment with PPIs at the lowest dose for the shortest amount of time, and thus may favour longer-term H2RA prescriptions"

We thank the reviewer for the suggestion to conduct a time-series analysis. This is ongoing work that has been submitted to a different journal. Given the extensive analyses and length of the current manuscript, we felt the time-series analysis was outside the scope of this paper.

Minor comments:

1. There are some grammatical errors/run-on sentences in the manuscript which could be revised for clarity and readability (i.e. Discussion paragraph 2: "While use of H2RAs may be associated with delirium and acute interstitial nephritis, they are generally well tolerated compared to PPIs, and are more commonly associated with mile adverse effects like headache and constipation, not the serious adverse effects associated with use of PPIs").

We have rewritten this sentence for clarity (Page 15, Paragraph 2):

"While use of H2RAs may be associated with delirium and acute interstitial nephritis, they are generally well tolerated. Indeed, H2RAs are more commonly associated with mild adverse effects like headache and constipation, not the serious adverse effects associated with use of PPIs"

2. Can the authors clarify whether the CPRD captures prescriptions written or dispensed, and add relevant limitations (i.e. if dispensed only, don't know about patient adherence; if prescribed only, don't know if patient filled prescription or adhered).

The CPRD captures prescribed medications only. We have added this to the Methods section (page 7, paragraph 1) and the discussion (page 17, paragraph 3):

"The CPRD contains information on demographics, diagnoses and procedures, and prescriptions issued by general practitioners are recorded using the British National Formulary."

"Prescriptions recorded in the CPRD are those issued by general practitioners, and thus it is not possible to assess patient adherence or determine if a patient filled a prescription."

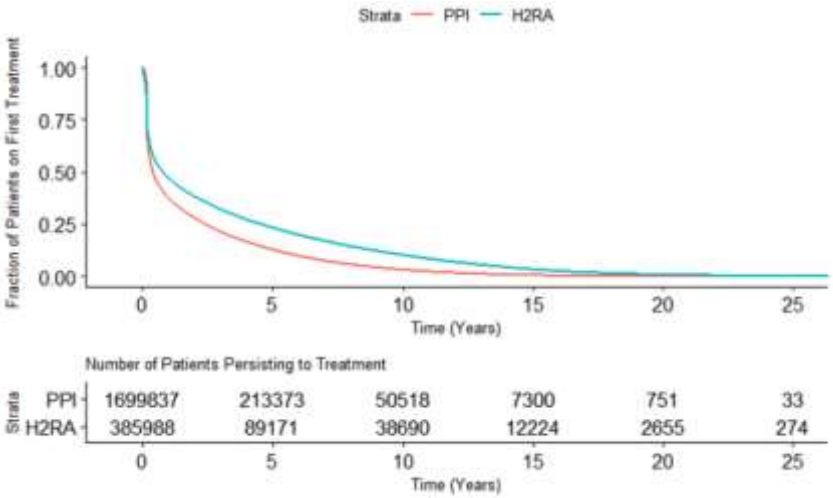
3. Results, paragraph 2: can the authors include the denominator for these percentages (ie number of people newly initiating an acid suppressant drug)?

Yes, we have added this information to Page 12, paragraph 2:

"Among patients newly-prescribed an acid suppressant drug (n=2,085,825), 81.5% (n=1,699,837) were initially prescribed a PPI, while 18.5% (n=385,988) were initially prescribed a H2RA"

4. Figure 4: I'd suggest presenting both drugs on the same curve in one figure to better allow for comparison. Removing symbols for censoring would also make the two lines easier to compare.

We thank the reviewer for this suggestion, which has improved the readability of Figure 4.



5. In Results paragraph 4, where Supplementary Figure 5 is discussed, the authors describe value per 1000 person years, where the Figure's y-axis is displayed in %. Can the authors clarify which measure was used?

Thank you for pointing this out. To be consistent with the rest of the figures, we have changed these values to percentages and updated the manuscript accordingly (Page 13, Paragraph 2):

"Throughout the study period, the prescribing intensity of PPIs ranged from 0.07% in 1990, increasing to a peak intensity of 0.98% in 2012 (**Supplementary Figure 6**). In contrast, the prescribing intensity of H2RA use decreased over the study period from the highest intensity of 1.95% in 1990, to the lowest intensity of 0.08% in 2013"

6. Results, Paragraph 5: The authors mention Supp Table 3 with the sensitivity analysis by varied definition of ongoing use, but don't summarize the findings at all. Inclusion of how the results shifted with changing definition would be helpful. Also – there is an error in Supp Table 3, under "7 day grace period" where the row titled "Treatment gap >60 days" should read "Treatment gap >7 days".

We have added a sentence to the results to contextualize these findings (Page 14, Paragraph 1) and corrected the typo in the table.

"When a grace period of 7 days was applied, the median (IQR) duration of PPI and H2RA use was 66 (36 to 560) and 149 (38 to 1,479) days, respectively. When a grace period of 60 days was used, the median (IQR) duration of PPI use was 231 (89 to 1,097) days, and H2RA use was 381 (91 to 1,785) days. The reasons for discontinuation according to these alternate grace periods were consistent."

7. Results, paragraph 5, the authors state that "H2RA users were equally likely to discontinue use due to a treatment gap exceeding 30 days, administrative censoring, or because of a switch to a PPI." It is easy for this to be misinterpreted as the reasons for discontinuation among H2RA users being similar to that of PPIs. I would suggest rephrasing (e.g. "In contrast, approximately one-third of H2RA users discontinued due to each of: treatment gaps exceeding 30 days, administrative censoring, or because of a switch to a PPI").

We have corrected the text for clarity according to the reviewer's suggestion (Page 13, paragraph 3):

"Approximately one-third of H2RA users discontinued use due to each of the following: a treatment gap exceeding 30 days, administrative censoring, or because of a switch to a PPI."

8. In the discussion, a citation would support the statement that "a significant portion likely represents overtreatment and failure to re-evaluate for ongoing necessity".

The discussion has been changed to reflect the stratified persistence patterns.

Reviewer: 3

Reviewer Name

Yasuhisa Sakata

Institution and Country

Saga University, Japan

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

This manuscript reported the trends of acid suppressant drugs over time in the UK.

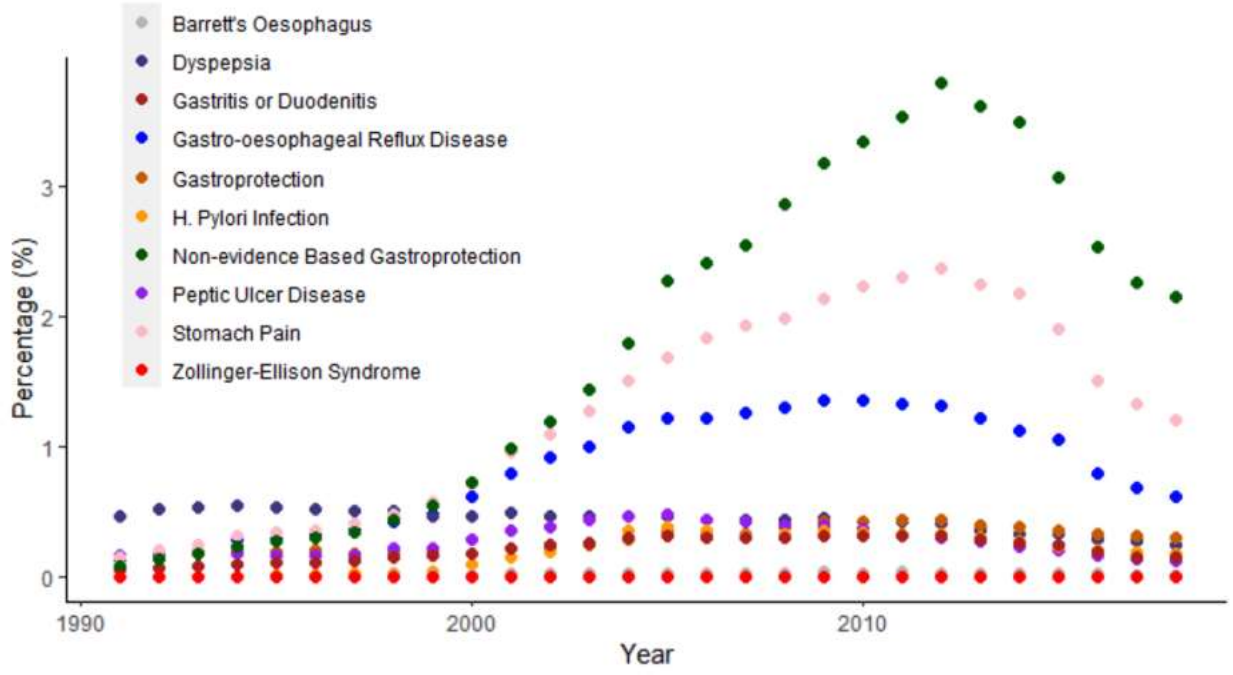
The authors found that prescribing intensity of H2RAs has increased over the last decade, while prescribing intensity of PPIs has plateaued in recent years. The findings are interesting, but I have some comments.

We thank the reviewer for the positive feedback and will address all comments below.

My comments are as follows.

1. This study demonstrates that the prevalence of PPI use has increased with time. Has the incidence of GERD or other acid-related disorders, most common indications for PPIs, been increasing with time in the UK.? In addition, has prevalence of NSAIDs or antiplatelet drugs been increasing in the UK?

We thank the reviewer for raising this important issue. Given that PPIs and H2RAs have the same indications, we investigated the overall incidence of these indications over time among new users of both acid suppressant drugs. To calculate incidence, we divided the number of patients newly diagnosed with each indication, separately, by the number of patients in the CPRD in each calendar year. As illustrated in Supplementary Figure 1, the majority of indications had consistently low incidence over time. The only evidence-based indication which moderately increased over time was GERD. These results are summarized in the manuscript on page 12, paragraph 2, and in the discussion on Page 15, Paragraph 2:



"The incidence of indications for acid suppressant use was relatively consistent over time, with gastro-oesophageal reflux disease the only evidence-based indication that slightly increased over follow-up (Supplementary Figure 1)."

"…it cannot be explained by an increase in the incidence of indications for PPIs and H2RAs, which have been relatively consistent over time."

2. Authors described that H2RA prescribing intensity has been increasing from 2010 probably following the new guidelines. Does this suggest that there are many patients whose symptoms improved even with H2RA?

The increase in intensity to H2RAs indicates that H2RAs are being more frequently. This may indicate symptom improvement, if patients are responding to treatment and are thus persisting to treatment for maintenance purposes. Alternatively, this could suggest that symptoms are not improving, which would require additional treatment. Given that the data does not allow us to make this distinction, we did not address this in the manuscript.

3. Do the new guidelines recommend a switch to H2RAs from PPIs if acid suppressant drugs are needed after the first treatment course of PPIs?

We thank the reviewer for highlighting this gap in knowledge in the original version of the text. Yes, the new guidelines recommend treatment with H2RAs for patients who do not respond to PPI treatment. We have added additional information to the manuscript to further contextualize the role of H2RAs. The full response for this query can be found above in responses to reviewer 2, major comment 7.

4. This study showed an increase in use of H2RAs among the paediatric population over the past decade. What could be the reason for this trend?

Figure 3 illustrates a slight increase in H2RA use among the paediatric population over the past decade. While the number of new H2RA users is the highest among the paediatric population (Supplementary Figure 3), this is not markedly different from the other age categories. This has been corrected in the manuscript to prevent the overinterpretation of results (Page 13, paragraph 1):

"Overall and sex-stratified prevalence of use were similar among new users (Supplementary Figures 2 and 3), though the prevalence of H2RA use among new users was consistent across all age categories over the past decade (Supplementary Figure 4)."

I hope these comments will be helpful.

We thank the reviewer for their comments.

VERSION 2 – REVIEW

REVIEWER	Tara Gomes St. Michael's Hospital, Canada
REVIEW RETURNED	28-Aug-2020

GENERAL COMMENTS	I'd like to thank the reviewers for their thorough responses to the reviews. I believe that they have adequately addressed all of my questions and believe that this is now suitable for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Comments to the Author
I'd like to thank the reviewers for their thorough responses to the reviews. I believe that they have

adequately addressed all of my questions and believe that this is now suitable for publication.

We thank the reviewer for their comments and positive feedback on our manuscript.