Author's response to reviews

Title: Online follow-up of individuals with gastroesophageal reflux disease using a patient-reported outcomes instrument: results of an observational study

Authors:

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Author's response to reviews: see over
Dear Tonilynn Manibo,

We would like to thank BMC Gastroenterology and are indebted to the reviewers for their time and energy devoted to our manuscript. We appreciate the constructive comments on how to improve our manuscript; they all have been addressed point-by-point in this cover letter.

**Reviewer's report 1:**

This is a study that documents to some extent the concept of defining groups of dyspeptic patients by internet surveys, and following up by repeated symptom questionnaires.

1. A main problem is selection bias, since particularly the PPI user group is likely to consist of PPI partial or non-responders, furthermore the study is for practical reasons open only to internet users. It can be argued that more people are internet users than are consulters for GERD (supported by the finding that only 37-45% actually visited their PCP).

We are aware that our study design is associated with certain limitations. We have a relatively high proportion of PPI users that are labeled as partial or non-responders. We assume that respondents who still experience symptoms, despite of acid suppressive treatment, will be more likely to complete our questionnaire. We have described this limitation in our Discussion section as follows: “However, including respondents online is associated with limitations, most importantly selection bias. We faced a high dropout rate, probably related to the noncommittal attitude of an online questionnaire and the fact that we asked respondents to complete a total of 4 questionnaires during follow-up.“

2. It must be emphasized that symptoms compatible with GERD is not a diagnosis, although GerdQ is designed to exclude dyspeptic symptoms of epigastric pain and nausea to some extent by weighting the negatively.

We agree with the reviewer that we cannot exclude any inclusion of individuals with other
diagnosis than GERD. We have described this limitation as follows in the Discussion section of our article:

“We also do not have additional information about the medical history, comorbidity and reports of any additional investigations, such as upper endoscopy. We therefore cannot exclude that we included individuals with other diagnoses than GERD, or with concomitant diseases in addition to GERD. “

3. The two patients groups cannot be compared, as all assessment variables and endpoints are different.

The majority of data in the previous version of this manuscript were nested analyses (within the same group). For example, we compared outcomes in non-PPI users at 4 and 12 weeks (Figure 2).

We have deleted results that compared PPI users with non-PPI users. Therefore, in the revised version only data within the same group are compared and described. Table 2 and 3 show reasons to consult a healthcare provider or to refrain consultation without any statistical comparison between both groups.

4. In non-PPI users, the definitions do not make sense, since small or larger changes in GerdQ score crossing (or not) the cutoff of "8" are all classified the same.

In the PPI users group, endpoints are more in line with what is used in clinical studies.

We used the GerdQ self-assessment questionnaire for the follow-up of included individuals. A previous study using the GerdQ concluded that a cut-off of 8 had the highest sensitivity and specificity, which was comparable with the diagnostic accuracy of a gastroenterologist [Jones et al, Development of the GerdQ, Alimentary Pharmacology&Therapeutics 2009]

We also used this cut-off value during follow-up to define “symptom improvement” in individuals without PPI use.

Spurred by the remarks of the reviewer we questioned our dataset in more detail. We followed 4 individual symptoms over time (heartburn, regurgitation, sleep disturbance, and OTC use).
Tielemans MM, van Oijen MGH. Online follow-up of individuals with gastroesophageal reflux disease using a patient-reported outcomes instrument: results of an observational study

See the Table below (Table 2 in the revised manuscript).

<table>
<thead>
<tr>
<th>Symptom frequency</th>
<th>0 days</th>
<th>1 day</th>
<th>2-3 days</th>
<th>4-7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heartburn during the preceding week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>25/403 (6.2)</td>
<td>46/403 (11.4)</td>
<td>152/403 (37.7)</td>
<td>180/403 (44.7)</td>
</tr>
<tr>
<td>4 weeks (%)</td>
<td>59/403 (14.6)</td>
<td>84/403 (20.8)</td>
<td>142/403 (35.2)</td>
<td>118/403 (29.3)</td>
</tr>
<tr>
<td>12 weeks (%)</td>
<td>23/140 (16.4)</td>
<td>40/140 (28.6)</td>
<td>41/140 (29.3)</td>
<td>36/140 (25.7)</td>
</tr>
<tr>
<td>24 weeks (%)</td>
<td>15/68 (22.1)</td>
<td>15/68 (22.1)</td>
<td>23/68 (33.8)</td>
<td>15/68 (22.1)</td>
</tr>
<tr>
<td><strong>Regurgitation during the preceding week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>124/403 (30.8)</td>
<td>136/403 (33.7)</td>
<td>82/403 (20.3)</td>
<td>61/403 (19.4)</td>
</tr>
<tr>
<td>4 weeks (%)</td>
<td>135/403 (33.5)</td>
<td>125/403 (31.0)</td>
<td>99/403 (24.6)</td>
<td>44/403 (10.9)</td>
</tr>
<tr>
<td>12 weeks (%)</td>
<td>61/140 (43.6)</td>
<td>40/140 (28.6)</td>
<td>26/140 (18.6)</td>
<td>13/140 (9.3)</td>
</tr>
<tr>
<td>24 weeks (%)</td>
<td>35/68 (51.5)</td>
<td>20/68 (29.4)</td>
<td>10/68 (14.7)</td>
<td>3/68 (4.4)</td>
</tr>
<tr>
<td><strong>Sleep disturbance during the preceding week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>81/403 (20.1)</td>
<td>108/403 (26.8)</td>
<td>136/403 (33.7)</td>
<td>78/403 (19.4)</td>
</tr>
<tr>
<td>4 weeks (%)</td>
<td>116/403 (28.8)</td>
<td>96/403 (23.8)</td>
<td>120/403 (29.8)</td>
<td>71/403 (17.6)</td>
</tr>
<tr>
<td>12 weeks (%)</td>
<td>49/140 (35.0)</td>
<td>36/140 (25.7)</td>
<td>34/140 (24.3)</td>
<td>21/140 (15.0)</td>
</tr>
<tr>
<td>24 weeks (%)</td>
<td>19/68 (27.9)</td>
<td>19/68 (27.9)</td>
<td>21/68 (30.9)</td>
<td>9/68 (13.2)</td>
</tr>
<tr>
<td><strong>OTC use during the preceding week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>107/403 (26.6)</td>
<td>68/403 (16.9)</td>
<td>117/403 (29.0)</td>
<td>111/403 (27.5)</td>
</tr>
<tr>
<td>4 weeks (%)</td>
<td>106/403 (26.3)</td>
<td>70/403 (17.4)</td>
<td>107/403 (26.6)</td>
<td>120/403 (29.8)</td>
</tr>
<tr>
<td>12 weeks (%)</td>
<td>39/140 (27.9)</td>
<td>30/140 (21.4)</td>
<td>33/140 (23.6)</td>
<td>38/140 (27.1)</td>
</tr>
<tr>
<td>24 weeks (%)</td>
<td>25/68 (36.8)</td>
<td>11/68 (16.2)</td>
<td>16/68 (23.5)</td>
<td>16/68 (25.3)</td>
</tr>
</tbody>
</table>

Indeed, the frequency of the 4 individual symptoms decreased during follow-up, but many
respondents still experienced symptoms during follow-up.
We also assessed mean scores of heartburn, regurgitation, sleep disturbance and OTC use within individuals over time with paired t-tests.

In addition to Table 2, we added the following text to the Results section:
“...In addition, we assessed 4 individual GerdQ questions during follow-up (Table 2). After 24 weeks, heartburn or regurgitation for a maximum of one day per week was reported by 44% and 81% of respondents without PPI use, respectively. Mean symptom frequencies of heartburn and regurgitation in non-PPI users significantly declined within individuals during follow-up from 2.21 at baseline to 1.43 at 24 weeks and from 1.20 to 0.77, respectively (both p<0.01). Mean symptom frequencies of sleep disturbance and OTC use in non-PPI users declined from 1.52 to 1.20 (P=0.30) and from 1.58 to 1.23 (p=0.67), respectively...”

5. All this leaves us with a pure feasibility study.

The aim of this study was to assess symptoms over time and to assess reasons for healthcare consultation in an Internet population with GERD. The use of Internet is a novel method to collect study information and gives us the opportunity to include individuals that are not reached by the traditional methods for inclusion and follow-up of a target population. The potential of the Internet for study purposes has not yet been fully developed. We finish our abstract and the Conclusion section of our manuscript with the statement that online follow-up is feasible, with the following text: “Online follow-up of an Internet population with GERD is feasible.“

6. In the "Statistical analysis" section, we are presented with more variables, which should have been in the Outcomes section, or elsewhere in a separate section.

We made some adjustments in the Statistical analysis section. We have depicted the content of this part of our manuscript below with specific reference where it can be retrieved from the manuscript text.
Baselines variables for respondents without PPI use and PPI users were assessed with descriptive statistics.

These results are described in the first paragraph of the Results.

Percentages of symptom improvement, stable symptoms and relapse were assessed separately for PPI and non-PPI users and were calculated with chi-squared analysis or Fisher exact, whenever appropriate. If one of the follow-up questionnaires was missing, data were compared with the previous completed questionnaire (e.g. if Survey C was missing, data of Survey D and B were compared).

These data are depicted in Figure 2 and 3.

Frequencies of heartburn, regurgitation, sleep disturbances and OTC acid suppressive medication use during follow-up were calculated with frequency tables in respondents without PPI use.

These data are depicted in Table 2.

Mean symptom frequency within individuals during follow-up was assessed by paired t-tests in non-PPI users.

These results are described in the Results section.

We analyzed respondents according to (non-) PPI use at baseline.

Respondents were asked at baseline whether they had intended to visit a healthcare practitioner. During follow-up we asked whether they had actually visited a healthcare practitioner.

These results are displayed in the Results, in the section: ‘healthcare consultation patterns’.

Reasons for consultation were assessed with closed questions and presented in frequency tables. If respondents performed more than one healthcare visit during follow-up, only reasons for the first visit were taken into account. In respondents that did not visit a healthcare provider during follow-up, reasons that were reported in the last completed questionnaire were included and depicted in frequency tables.

See Table 3 and 4.

Associations between outcome at 24 weeks and GerdQ score at baseline and type of symptom at baseline were analyzed with chi-squared analyses.
This refers to the following sentence in the Results section: “Neither individual symptoms nor GerdQ scores at baseline were associated with symptom improvement at 24 weeks in respondents that did and did not use PPIs.”

We also analyzed the percentage of respondents that started or stopped their PPI with descriptive statistics. For this analysis, we only took the first medication switch into account. A per protocol analysis was performed, including only those respondents who did not change their use or non-PPI use during the 24-week follow-up.

The results of these analyses are stated in the paragraph above ‘healthcare consultation patterns’.

Reviewer’s report 2:

Some Minor Essential Revisions have to be done:

1. Second page-At the beginning of new sentence in the 6th line of results authors have to correct 55% in Fifty-five percent.

   Thank you for mentioning this typo. We have changed 55% in Fifty-five percent.

2. Citation of references 3 and 12, need correction and true citation as The New England Journal of Medicine.

   We have changed these citations.

3. Correct citation of references 6,10,15,16,17,21,22,23,24,25 is Alimentary Pharmacology&Therapeutics or shorten Aliment Pharmacol&Ther.

   We have changed these citations into Alimentary Pharmacology&Therapeutics.

4. In relation of policy of citation of BMC Gastroenterology for multiple authors, if the number of cited authors is 10, then authors of article are correctly do that. In the case the number of authors are 4 or 6 than authors need to change corrections in a few references.

   We have verified the number of authors in all citations. Only reference 23 has more than 10
authors. We, unfortunately, do not understand the request stated above. Therefore, we did not make any changes to this reference.

5. In reference number 4 authors cited French name of Canadian Journal of Gastroenterology as English. English name is sufficient.

We have changed this citation into Canadian Journal of Gastroenterology.

6. In reference 2, after Melton LJ, 3rd need to delete.

Done

7. In references 7 and 19 after volume there are only first page of article.

We have referred to Reference 7 as is suggested in this article and therefore did not change this citation. (Bruley des Varannes S, Lofman HG, Karlsson M, Wahlqvist P, Ruth M, Furstnau ML, Despiegel N, Stalhammar NO: Cost and burden of gastroesophageal reflux disease among patients with persistent symptoms despite proton pump inhibitor therapy: an observational study in France. BMC gastroenterology 2013, 13:39.)

This is the same for Reference 19 and therefore we also did not change that citation. (Shaw M, Dent J, Beebe T, Junghard O, Wiklund I, Lind T, Johnsson F: The Reflux Disease Questionnaire: a measure for assessment of treatment response in clinical trials. Health and Quality of Life Outcomes 2008, 6:31.)

8. In reference 7 After BMC G in gastroenterology need to be in block letter.

Done

9. Citation of reference 18 is not complete. Fail number of pages.

This reference does not have any page numbers. Therefore, we were not able to change this reference.

10. Reference number 27 is not complete and need to be changed with addition of
Tielemans MM, van Oijen MGH. Online follow-up of individuals with gastroesophageal reflux disease using a patient-reported outcomes instrument: results of an observational study

netherlands as language of reference.

We have changed this reference into:

11. In references 8 and 19, first block letter in the name of references need to be done.
12. The same corrections should be done in references 9, 14, and 26.

Done