Author's response to reviews

Title: How do COPD patients respond to exacerbations?

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Author's response to reviews: see over
Dear editor,

Many thanks for this peer feedback procedure and the opportunity to revise our manuscript.

Hereby we provide a point-by-point response to the concerns of the editor and the two reviewers. We made the following revisions (red font):

**Reviewer 1.**

The paper is interesting, innovative, well-written and pertinent. The authors wanted to investigate patient’s decisions and self-management behavior during symptomatic days and exacerbations episodes. This topic is very important since some recent papers have alerted about the high percentage of unreported exacerbations among COPD patients. I have no major comment. Only some minor issues have been submitted to the authors. In my opinion if they could address these minor aspects it will make this paper more understandable for the readers.

**MINOR REVISIONS:**

1. When the authors refer to the attention on energy conservation I would encourage them to explain it more thoroughly, at least the first time they refer to it in the Introduction. They have to explain why they take the three types of action into account.

We agree with reviewer 1 that the ratio behind the types of actions needs to be clarified. In a multinational interview-based study in CHEST 2006, Kessler et al. reported that energy conservation (Resting, lie / sit down, stay calm etc.), taking medication and contacting healthcare providers were the most frequent actions taken by patients. To meet the concerns of the reviewer, we added:

**Last paragraph of the method section**

“Selection of these actions was made according to a large multinational interview-based study in which patients were asked to retrospectively report on exacerbation experiences [18].”

The term energy conservation was used as a surrogate for ‘planning periods with rest’, which was the question used in the diary. Also in response to concern 7 of reviewer 2, we think the term energy conservation is confusing. Therefore we replaced ‘energy conservation’ by ‘planning periods of rest’ in:

**2nd paragraph of the abstract**

**2nd paragraph of the method section**

**Last paragraph of the method section**
2. The authors have to explain why so many patients did not want to participate in this short follow-up study. They are talking about some reasons—for instance, 36 patients were unmotivated—but they fail to explain more in-depth the reasons why they dropped out. I encourage the authors to comment on this issue, particularly, they should explain or better change the sentence ‘a convenience sample of COPD patients were recruited’.

It needs to be emphasized that the 36 non-motivated patients are actually non-participants and not drop-outs. Although these patients were eligible according to pre-defined criteria these patients did not provide their consent. Within these non-responders we were only able to distinguish the following reasons: 1) feeling to ill, 2) not motivated and 3) other. For observational studies where patients are asked to answer questions on a daily basis, a response-rate of 69% can be considered acceptable not hampering the external validity of the study. Like many studies, sampling was based on patients voluntarily agreeing to participate resulting in a convenience (non-probability) sample of COPD patients. Still, we agree with reviewer 1 that the term ‘convenience’ might be unnecessarily confusing. Therefore we made the following changes:

1st Paragraph of the methods section

We changed:

“Between January and March 2008, a convenience sample of COPD patients were recruited from inpatient (post-discharge) and outpatient clinics from the University Medical Hospital…”

Into

“Between January and March 2008, COPD patients were recruited from inpatient (post-discharge) and outpatient clinics from the University Medical Hospital in Utrecht…”

3. They do not comment on the quality of the diaries. One of the limitations of this type of studies, in which symptom diaries are used, is their quality. They say that 9% of diaries were incomplete. Even though the follow-up was actually short, only six weeks, I find this percentage too low. I would like to know the values omitted in the remaining diaries and their quality. I consider that the authors should be more cautious and be humble when addressing this issue.

Reviewer 1 addresses an important aspect of valid exacerbation assessment. We agree that 13 patients (9%) is relatively low. However, as stated in the method section, we incorporated methods to enhance validity and completeness of diary recording. Patients were contacted by the investigators by telephone after the first 7 days to review their compliance and understanding with regard to the daily assessments. In these contacts, patients were explicitly instructed and reminded to fill in each question every day. In a recent paper (Trappenburg et al. Eur Respir J. 2011 May;37(5):1260-8) we have addressed the importance of these methods.

4. I would like to know if there were any differences in the outcome variables between patients discharged from hospitals and those who attended the outpatient clinics. Since the authors have got the information about the lung functional status of these patients I would like to know the differences observed between the subjects with a more conserved functional status and those with lower FEV1 measurements.
We believe the results in table 2 answer the request of reviewer 1. In this table, outcomes are reported by disease severity, expressed by FEV1%pred and hospital admissions in the previous year. A sub-group analysis attempting to answer the question regarding difference in recruitment would surely be criticized for its lack of statistical power, particularly since the ratio of patients with at least one exacerbation was 62/13 (scheduled visit / post discharge).

Reviewer 2.

This is an interesting and well written article addressing the important issue of patient self management in the event of symptom deterioration in patients with COPD. The limitations are discussed well in the discussion; however the methodology is quite confusing.

Major compulsory revisions

1. The definition of exacerbation quoted is incorrectly referenced. The authors state that patients required 3 major symptoms or a major and minor and reference the London cohort but this was NOT the definition used by the London COPD group. This is also confusing with respect to grading of exacerbations as according to the authors definition a type 4 exacerbation will not have been counted as an exacerbation.

Symptom-based exacerbation assessment requires appropriate methods of diary recording and a valid symptom-based algorithm (Trappenburg Eur Resp J 2011, Effing Chest 2009). We do not agree with reviewer 2 that our definition required 3 major symptoms or a major and minor. In the method section we stated:

“Exacerbations were defined according to previously accepted criteria[3,8,15] if the following symptom patterns were experienced for at least two consecutive days: either two or more of three major symptoms or any one major symptom together with any one of the minor symptoms.”

Nevertheless, we fully agree with reviewer 2 that referring to the ‘East-London algorithm’ (modified Anthonisen) is confusing and inconsequent since we also evaluated type-4 events. The latter are events without minor symptoms and technically do not meet the ‘Modified Anthonisen criteria. Instead of stating that we applied the Modified Anthonisen algorithm and added type 4 events, it’s better to quote our definition based on the lowest threshold of 1 major symptom (for two consecutive days) without a minor symptom. To meet this important comment we made the following changes:

“Exacerbations were defined according to previously accepted criteria[3,8,15] if the following symptom patterns were experienced for at least two consecutive days: either two or more of three major symptoms or any one major symptom together with any one of the minor symptoms.”

Changed into

“A symptom-based exacerbation was confirmed if, for at least two consecutive days, patients experienced a worsening of at least one of three major symptoms (increased sputum amount, changed sputum color / purulence, and increased dyspnea).”

2. The authors mention the collection of symptom scores in the methodology but they are not discussed in the results. There is no mention of symptom score with relation to type of actions for example.
The symptom count (summed score ranging from 0-11) at onset was analyzed and reported in the result section in table 2.

3. There is no a priori hypothesis stated or power calculation.

In the last paragraph of the introduction we stated the hypothesis that “whilst not contacting a healthcare provider in the event of an exacerbation, patients might take other types of self-management action”. Initially, this study did not aim to test this hypothesis, and therefore is lacking an appropriate a priori power calculation. Data were obtained from a pilot-study aiming at the development of an Action Plan for COPD patients. As stated in the limitation section (discussion), the number of events per predictor variable did not reach the rule of thumb to allow for multivariate logistic regression analysis. Unfortunately, the present study could solely evaluate the association between single characteristics and actions taken.

4. Please provide confidence intervals instead of standard deviations.

Good suggestion of reviewer 2. Therefore we made the following changes:

Table 2
All ± SD values were re-calculated and replaced by confidence intervals.

Table 2 Annotation
We added: “Data are expressed as Mean (95%CI), Median [Interquartile range] or count (percentage).”

Results, second paragraph of the ‘actions take by patients’ section
Standard deviations are replaced by confidence intervals

5. It is possible that some of the statistical findings in the reulsts may have occured by chance, e.g. current smoking and energy conservation. The results should be discussed with respect to underlying hypothesis and not just in terms of a significant p value.

We agree with reviewer 2 that the results of this univariate analysis need to be interpreted with caution (and like other underpowered studies, may have occurred by chance) as we stated in the discussion section. However, in our study, we are 95% confident that current smoking was associated with a higher likelihood of less appropriate self-management behaviour (both energy conservation as inhalator use). We believe this is carefully discussed and externally validated in the 5th paragraph of the discussion section. However, a study with larger sample size would not only allowed multivariate analysis of determinants but also to adjust for potential confounders. The latter is important to validate our indicators of appropriate self-management behaviour. Therefore we added:

7th paragraph of the discussion section
“Adequately powered observational studies allowing multivariate analysis including adjustment for potential confounders are needed to validate current indicators of self-management behaviour.”

Minor essential revisions
5. The title is very vague. It is not clear what constitutes a timely measure or what a period of symptom deterioration is. If it is an exacerbation, than this should be stated.

We agree with reviewer 2 that the title of this manuscript can be more specific. Therefore we changed the title into:
How do COPD patients respond to exacerbations?

6. The first sentence of the abstract is incorrect. It is stated that “exacerbations seem clinically important”. It is well known that exacerbations are clinically important events.

We believe that reviewer 2 might have read this sentence slightly wrong, since it states that “timely treatment of COPD exacerbations seems clinically important” instead of “exacerbations seems clinically important”

7. Please define energy conservation.

We hope our response to the 1st comment of reviewer 2 sufficiently addresses the reviewers concern on energy conservation.

8. The patients are recruited from very different environments; post discharge from hospital and outpatient settings leading to a very diverse group. Patients recently discharged from hospital may be more educated about exacerbations as they have recently had one and may be more likely to notice symptom changes and do something about it.

We like to refer to our response to the 4th comment of reviewer 1 in which we address differences in recruitment and previous exacerbations/admission.

Discretionary revisions
9. The use of a convenience sample of patients is not ideal and may introduce bias.

For this comment on how patients were sampled we like to refer to our response to the 2nd comment of reviewer 1.

10. 6 weeks is not a long period of time but the authors do discuss this in the paper.

The relatively short follow-up period is discussed in the 2nd limitation of the discussion section.

11. This is not strictly speaking a cohort study.

We agree that this study is strictly not a cohort study but an observational study with repeated measurements. To prevent confusion, we changed cohort by observational in:

2nd paragraph of the abstract.

Last paragraph of the introduction

2nd paragraph of the method section

We hope we have addressed all queries of the reviewers adequately. We have revised the manuscript to the best of our knowledge and hope you will consider this manuscript (including revisions) for publication.

We are looking forward to your response.

Yours sincerely

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