Author's response to reviews

Title: Reliever salbutamol use as a measure of exacerbation risk in chronic obstructive pulmonary disease

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

Thank you for the opportunity to review the manuscript by Jenkins et al, “Reliever salbutamol use as a measure of exacerbation risk in chronic obstructive pulmonary disease.” In this retrospective cohort analysis, the use of rescue inhaled short acting bronchodilators was assessed as a predictor of exacerbation in subjects with moderate to very severe COPD. This is a well-written manuscript that addresses an important knowledge gap, the ability to identify COPD subjects who are at risk for exacerbations.

Overall, while I think that this paper does a good job addressing this issue, I would not recommend acceptance in its current form. However, after addressing the issues below, I would find this a potentially useful analysis.

Major compulsory revisions:
1. Study population:
The authors wish to examine the utility of recent rescue inhaler use as a marker of future exacerbation risk. However, I am concerned that the study population that they are using does not represent the general COPD population and therefore limits interpretation and overall generalizability. I would recommend the authors address the following issues regarding their study population both in the methods and discussion:

   We acknowledge the reviewer’s concern about the generalisability of our findings and emphasise in the paper (line 293–9) that testing in a larger population with milder patients would help address this.

2. The subjects were enrolled in a study in which they were asked to discontinue their usual COPD medications, and start LABA or LABA/inhaled CS. Prior data suggests discontinuing inhaled CS could predispose to exacerbations, and in fact the LABA alone group did seem to have more exacerbations, as was noted in the original paper. Additionally, the single use of just LABA in severe to very severe COPD is not recommended by treatment guidelines, and therefore this does not represent ‘real world’ standard of care. These facts limit the interpretability of findings in the LABA group. Could the authors limit their main analysis to the BUD/FORM group alone?

   This was a retrospective analysis of a previously conducted clinical study, of which the aim was to assess the differences between ICS/LABA and LABA. The inclusion of both treatment groups in the present analysis allowed the comparison of reliever use in patients randomised to two different drug classes, and we believe that restricting the analysis to the BUD/FORM arm would not improve the paper. However, that LABA alone is not recommended and the limitations of this analysis have been added in lines 324–330:
As with the original study,[16] it is unclear whether discontinuation of inhaled corticosteroids in those patients who received FORM alone contributed to worse exacerbation outcomes compared with those receiving BUD/FORM. Long-acting β₂-agonist monotherapy is not recommended in patients with severe-to-very-severe COPD, limiting the interpretability of our data in the FORM only group. We note, however, a trend to undertake studies assessing bronchodilators alone even in severe/Group D patients, so the issue of a non-inhaled corticosteroid approach to Group D – especially those who do not exacerbate frequently – is still being discussed.

While the reviewer’s comment regarding ICS use is important, we would like to clarify that ICS were used in only 27.8% of patients before study run-in (lines 205–6).

3. The subjects at baseline appear to have a very high frequency of rescue inhaler use, suggesting poorly controlled COPD. Standard of care would be to add additional COPD medication at the point that rescue inhaler use reaches greater than 4x/day, but it is unclear from this manuscript if subjects did experience escalation of care at that point. The authors could report medication use prior to study enrollment, or again, limit their analysis to just those subjects on BUD/FORM. A further sensitivity analysis might include only those subjects who had < 4 rescue inhaler uses/day at initiation of study.

1. Medication was not escalated following poorly controlled COPD. A note to this effect and details of additional medications allowed during a COPD exacerbation have been added in lines 135–8.

   “Medications were not escalated during the trial; however, medications allowed during a COPD exacerbation were oral corticosteroids, single injection parenteral corticosteroids (not depot formulations), xanthines, and inhaled or nebulized ipratropium or β₂-agonists”

2. Data for the most common COPD medications before run-in (n [%]) have been added to Table 1 and lines 205–6:

   “27.8% of patients received inhaled corticosteroids before study run-in (BUD/FORM: 26.5%, FORM: 29.0%).”
3. A sensitivity analysis has been added for long-term (3–12 months) exacerbation rates for patients with mean number of inhalations less than, and greater than or equal to, individual cut points of 0–12 inhalations/day in the week preceding the 2-month visit. The methodology (lines 184–6) and results have been updated with this analysis (lines 241–3), and a new Figure 2 has been added.

**6. Statistical analysis:**

It is unclear how the authors identified the inhaler use cut-off points, and how many subjects were in each cut-off. Could the authors perform a propensity score analysis or some other method that would allow them to identify cut-off points in an unsupervised manner, and then test the validity of these cut-off points as predictors of exacerbation in another population? Alternatively, is there a certain threshold that would predict future exacerbations? The authors’ extensive clinical expertise should not be discounted, however it may introduce some bias in to the analysis.

| 1. The numbers of patients in each reliever use group are added to the below sentence in the manuscript (lines 207–214). |
| **“Data were available for 807 patients in the short-term exacerbation risk analysis: 692, 351, and 91 patients reached the low (>4 inhalations/day), medium (>10 inhalations/day), and high (>20 inhalations/day) reliever use thresholds, respectively (patient n values are cumulative, i.e., all patients in the >20 subgroup are also in the >4 and >10 subgroups). In addition, data were available for 674 patients in the long-term exacerbation risk analysis: 234, 155, and 92 patients reached the mean number of inhalations/day for inclusion in the low (2–5 inhalations/day), medium (6–9 inhalations/day), and high (>10 inhalations/day) reliever use subgroups, respectively.”** |
| 2. The aim of the analyses was to investigate whether reliever medication use predicted short- and long-term exacerbation risk and not to identify and validate cut-off points; hence, reliever use categories were defined empirically based on the authors’ clinical experience. As such, a propensity score analysis to identify cut-off points and test the validity is beyond the scope of our analysis and should be investigated in future analyses. We have added the below text in lines 307–9 which discuss that future |
studies should validate reliever use groups.

“The reliever use categories in the present analysis were defined empirically to broadly reflect use in clinical practice based on the authors’ clinical expertise, and future analyses should validate reliever use categories to identify specific thresholds that may predict future exacerbations. However, even in the absence of further validation,...”

<table>
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<th>Minor essential revisions:</th>
<th>Details of the severity of patients from the original study are included in lines 123–4:</th>
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<tr>
<td>2. Study design and methods:</td>
<td>“in patients with moderate-to-very-severe COPD who had a history of one or more exacerbations in the previous year”</td>
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<tr>
<td>Lines 103-114-Please clarify which subjects were included in this analysis, including how their COPD was staged.</td>
<td>Lines 144–7 have been amended to clarify which patients from the original study were included in the current analysis:</td>
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<td>“Patients receiving twice-daily BUD/FORM pMDI 160/4.5 μg × 2 inhalations (320/9 μg) and formoterol dry powder inhaler (DPI) 4.5 μg × 2 inhalations (9 μg) were included in the present analysis. Patients receiving the lower dose of BUD/FORM were excluded from the present analysis as it is not a registered product.”</td>
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<td>2b. Did the authors adjust for additional covariates in their analysis such as smoking or age?</td>
<td>The analyses were not adjusted for additional covariates. A sentence to this effect has been added in lines 188–9.</td>
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<td>“The analyses were not adjusted for additional covariates.”</td>
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<td>3. Results p 10, lines 153-156; Table 1:</td>
<td>No statistical analysis was performed on the demographic data. We have amended the wording of lines 206–7 to match that of the original study:</td>
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<td>The authors report that there were no baseline differences between the BUD/FORM and BUD groups, however they do not present P values in this table.</td>
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"Demographic and baseline clinical characteristics of patients included in this post-hoc analysis generally were similar across treatment groups (Table 1).

4. Table 1: Could the authors present the number of subjects who fall in to each arbitrarily defined rescue inhaler cut-off point at the beginning of the study?

Patient numbers in each reliever use group have been added in lines 207–214.

5. Figure 2b is confusing, and I would suggest an alternate means of presenting this information.

Figure 2b has been removed and the data presented in the new Table 3. Please note patient n values in this table are cumulative (i.e. all patients in the ≥10 group are also in the ≥2 and ≥6 groups) and represent the number of patients remaining in the analysis for the week before the 2-month visit. A note to this effect has been added in the footnote of Table 3.

Reviewer 2

The authors performed a retrospective analysis of a study comparing budesonide/formoterol with formoterol and patients with moderate to very severe COPD and assessed the use of rescue beta agonist to a certain risk of exacerbation in the immediate (3 weeks) and long-term future (10 months). This is a very timely study as there are few indicators of an impending reported exacerbation other than use of daily symptom charts which are not very practical in the real world. The idea is similar to symptom/medication use report in bronchial asthma; this has proved very useful for assessing asthma control. I do have a few comments.

Major:

1. The author should clarify why 3 weeks and 10 months for chosen for time periods. While 10 months might be due to the overall duration of the study, 3 weeks needs to be explained better.

The 3-week time period was empirically defined and considered both the longest period of time following deviation from daily reliever use and the known evolution of COPD exacerbations. A note to this effect has been added in lines 157–60:

“Both the reliever use thresholds and 21-day time period were defined empirically; the reliever use thresholds broadly reflected use in clinical practice based on the authors’ clinical expertise, and the time period considered
both the longest period of time following deviation from daily reliever use and the known evolution of COPD exacerbations.[17]"

A 10-month time period was chosen to allow the longest time period between the 2 month visit and study end. A note to this effect has been added in lines 181–4.

2. The definitions for low medium and high reliever use or different for short-term and long-term exacerbation risk determination. Please clarify why this is the case.

This was a statistical judgment based on the data available. However, lower thresholds are used in the long-term definitions as they are an average of a week’s use preceding the 2-month visit, and daily levels would unlikely be >20 inhalations/day for a whole week. This has now been clarified in lines 157–60 and 181–84.

3. Can the authors provide quantification of risk in the short-term similar to data provided for long-term risk (21, 67 and 135%).

We thank the reviewer for their suggestion. Quantification of long-term risk reductions is possible as the analysis was based on exacerbation rates; however, the short-term analysis of risk is based on time to first exacerbation analysis with Kaplan-Meier curves testing for homogeneity between all curves, and we are unable to calculate derive ratios based on the comparison of three separate curves. As such, no change has been made.

4. The authors should perhaps provide incidence risk ratios as they adjusted for exacerbation clustering using Poison regression. When calculating the incidence risk ratio, did they correct for the number of exacerbations in the year prior to enrollment? History of previous exacerbations is one of the most important predictors of future exacerbations, and this will be important information to note.

We believe that incidence risk ratios are beyond the scope of the analysis as the two treatment groups had similar history of previous exacerbations in the past 12 months (Table 1), and correction for number of exacerbations was not necessary. Reliever use was a predictor of short- and long-term exacerbation risk independently of previous exacerbations.

5. The authors also had access to symptom charts and PEFR measurements. They should comment on how rescue inhaler use correlated with the above measurements.

We thank the reviewer for their suggestion. Although interesting, we believe that the suggestion is beyond the scope of the manuscript, which focuses on exacerbation
risk, and these variables should be investigated in future analyses.

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<td>1. Line 134: The authors perhaps mean 0 inhalation as reference group and not &gt; 0.</td>
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≥0 patients represents all patients included in the analysis and is used as a reference group. Line 157 has been clarified to:

“with ≥0 inhalations (i.e. all patients) as a reference group”

**Reviewer 3**

**Comment to authors**

I would like to thank for the opportunity to review this interesting paper. This paper is a new attempt to the prediction of progression from everyday indicators. I would like to make the following comments:

**N/A**

**Major Compulsory Revisions**

- **Page8, line131**
  - Why short period is 21 days? Please show a clearer reason.
  - The reasons for the time periods used in our analysis are discussed in response to reviewer 1’s above comments and have been added in lines 157–60.

- **Page10, line 158**
  - How much is the number of each groups of reliever use? I want to know how much the patients are using a large amount of reliever. Patients of higher reliever use may not prescribe appropriate treatment. Do you think that there is such a possibility?
  - Patient numbers in each reliever use group have been added in lines 207–14.

**Minor Essential Revisions**

- **Page10, line169**
  - “135%” is typo?
  - The 21%, 67%, and 135% greater exacerbation rates are relative to the <2 inhalations/day group. This has been clarified in lines 225–40:
    
    “Patients with a mean use of 2–5, 6–9, and ≥10 inhalations exhibited 21%, 67%, and 135%, respectively, greater exacerbation rates in the following 10 months relative to patients with a mean use of <2 inhalations/day”.

**Table1**

- “Patients taking ICS at baseline” 225 (2.8) # (28) typo?
  - The text has been corrected to:
    
    (2.8)

**Discretionary Revisions**

- **Page8, line133~**
  - The aim of our manuscript was to determine whether increasing reliever use increased short- and long-term
<table>
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<th>Page13, line212~</th>
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<td>As you say in Discussion part, I do not know whether this cut off point is appropriate. How about if you try the ROC analysis for the presence of exacerbation on the basis of the number of reliever uses?</td>
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<td>exacerbation risk, and not to validate reliever use categories. Future analyses and studies should validate reliever use categories to expand on our initial findings. A note to this effect has been added in lines 307–9:</td>
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<tr>
<td>“The reliever use categories in the present analysis were defined empirically to broadly reflect use in clinical practice based on the authors’ clinical expertise, and future analyses should validate reliever use categories to identify specific thresholds that may predict future exacerbations.”</td>
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<td>Page13, line212~</td>
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<td>In the cases with LAMA and LABA (+ICS) combination therapy, the frequency of use of SABA might change. In the future, you should be also consider the case where a combination of LAMA not only ICS / LABA.</td>
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<td>We thank the reviewer for this important recommendation. Lines 298–306 have been amended to:</td>
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<td>“In addition, further studies would enable assessment of the degree of individual variability and clarify the ideal reliever use cut-points in predicting COPD exacerbations. We wished to validate our findings in a larger study population receiving similar BUD/FORM and FORM doses and recording reliever use, using data from five randomized controlled trials of BUD/FORM [22-26] including the use of BUD/FORM in combination with a long-acting muscarinic antagonist.[22] However, methodological differences between the studies, specifically a mix of methodology (paper versus electronic diaries, different study duration and devices), meant that this analysis could not be undertaken in a suitably rigorous manner.”</td>
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