Author's response to reviews

Title: COPD related fatigue: Evaluation of factors associated with fatigue in COPD and comparison with healthy elderly subjects

Authors:

Agnieszka Lewko (agnieszka_lewko@yahoo.co.uk)
Penelope L Bidgood (bidgood@kingston.ac.uk)
Rachel Garrod (rachel.garrod@nhs.net)

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Author's response to reviews: see over
To the Editorial Board,
*The BMC Pulmonary Medicine*

Dear Editor,

In reply to your email from 13th August 2009 regarding the manuscript no 1472934868277512 entitled “COPD related fatigue: Evaluation of factors associated with fatigue in COPD and comparison with healthy elderly subjects”, we enclose the revised version of the manuscript. All reviewers’ queries have been addressed and a point-by-point response is provided below.

In response to one reviewer’s comment, the main title has been altered. Hence in reference to the manuscript the new title will be used “Evaluation of psychological and physiological predictors of fatigue in patients with COPD”.

The reviewers’ comments are marked in bold, whereas alternations and additions to the manuscript have been marked as underlined text. Following your suggestions, the format of the manuscript has been revised according to the journal guidelines.

Thank you for your time and consideration. We look forward to your reply,

Sincerely Yours,

Agnieszka Lewko
Penelope Bidgood
Rachel Garrod
Authors’ response to the reviews.

Version 2, Date: 3rd September 2009

Reviewer 1 comments response:

Specific comments:

1. Title is excessively long and should be shortened. In my opinion, the “comparison with healthy subjects” is not necessary at this level.

Title has been changed to: Evaluation of psychological and physiological predictors of fatigue in patients with COPD

2. More emphasis should be made on the clinical applicability and potential benefits to both the patients and physicians of the study results. As abovementioned, the study appears to be well conducted from a methodological standpoint, but it suffers from a clear emphasis in its potential beneficial effects at the clinical practice.

Clinical applicability has been explained in the Background section:

Although fatigue in COPD is acknowledged by clinicians, it is often neglected. In fact, compared with cancer the predictors and patho-mechanisms of fatigue are poorly evaluated in COPD and there is a lack of understanding regarding the management of fatigue, and further discussed (see below in point 8)

3. Rationale and hypothesis for conducting the study should be made more explicitly in the Introduction.

Rationale and hypothesis have been explained in the Background section by additional sentences:

There are few studies that comprehensively investigate predictors of the different domains fatigue in COPD. This study attempts to draw together the psychological and physiological aspects of fatigue to develop working models of COPD-RF, by using comparative data from healthy age-matched subjects. This research hypotheses that each component of increased fatigue in COPD may be predicted by differing factors.

4. Was ethical approval obtained from the institutional boards before carrying out the study? In keeping with, did patients and control subjects give their written informed consent before entering the study? Were all they properly informed
on the characteristics of the study? This is clearly missing from the current version, and this is important when working with living beings.

The information about ethical approval and written informed consent have been addressed in the Methods section: page 4, paragraph 1.

5. I wonder whether this investigation actually fits within the scope of the Journal, since the clinical relevance of this tool is not clear, or at least to this reviewer.

There is information about the MFI 20 tool validity in COPD population in the Background section:
…the Multidimensional Fatigue Inventory (MFI 20) [12], which is well validated in COPD [10,13]...

and in the Methods section, Subjective fatigue a sentence has been added:

Fatigue was assessed in the morning prior to other assessments in patients and healthy subjects using MFI 20, a 20-item self-report validated instrument [12,18]. The tool has been previously used in COPD population and it is recommended as an outcome measure in clinical settings [19].

6. I found the Results section somehow confusing and excessively long, especially because most of the study data are already shown in both Tables and Graphs. This section needs improvement and reduction of its length. Figures should be accompanied by legends; at least I have not seen them.

The results section has been shortened by:

• reducing amount of text in sub-sections: Comparative data, Fatigue and disease severity
• deleting Figure 2
• moving the important results from a text body to table 1.

For a better clarity the Predictors of fatigue in COPD subsection has been moved from the beginning to the end of the Results section.

7. A summary of main findings would also be very useful

Summary of main findings has been added:

Summary:
Fatigue score was significantly higher in COPD compared to control group for all dimensions of MFI 20. After stratification for MRC and GOLD classifications there were significant differences only for selected dimensions of fatigue. Fatigue, when considered as a multi-component construct was explained by a different combination of variables.

8. In the Discussion, more emphasis on the clinical applicability of the models analyzed should be made throughout.

In the Discussion more emphasis on clinical applicability of models analyses has been made by additional sentences:

Since fatigue is not routinely assessed in current clinical practice, the models from this study may help to identify patients who are at risk of being fatigued and develop effective fatigue management strategies. Furthermore, the regression analyses revealed that each component could be explained by different variations. Hence, the multi- rather than uni-dimensional assessment be considered.

9. It should also be underscored that the present investigation has been exclusively supported on the basis of pharmaceutical companies.

Competing interest section has been revised to address specifically the role of pharmaceutical companies. The companies were not involved in collection or analysis of this study data. The sponsor paid for one year stipend of Ms Lewko PhD to conduct other small project for GSK.

This project was part of Ms Lewko’s PhD, which was in part funded by GlaxoSmithKline (GSK).

Reviewer 2 comments response:

Major Compulsory revisions:

1. Please clarify how the 9 possible predictors were identified. It is very unclear why MRC dyspnoea was not included in the regression analysis. This is especially so as there were significant differences in General, Physical Fatigue and Reduced Activity according to MRC dyspnea. Dyspnea is also a very clinically relevant variable that can respond to intervention, thus possibly impacting fatigue. Please add information such as correlation information or additional rationale for excluding it in the regression.

Explanation how predictors were identified has been further developed by additions in the Methods section, Statistical analysis: Explanatory variables that were independent of one another, according to appropriate correlation tests were included
in the initial regression models. Other, clinically relevant variables, as identified from literature [9,10,17,30,13,31,32] were also included. The final models, presented here, are those where all the remaining independent variables are statistically significant predictors of the fatigue dimension under consideration and which have the highest $R^2$ value.

and in the Results section, Meaningful variables for fatigue dimensions

Clinically relevant variables were identified based on literature and results of correlations with fatigue dimensions. Following the initial regression analyses nine possible predictors were identified: % predicted FEV$_1$, depression, muscle torque, ISWT, end exercise SpO$_2$, IL6, Borg RPE, BMI, age. The final decision on which variables to include was determined by clinical relevance and by the best possible model of predictive variables.

Further explanation for not including MRC dyspnoea in the regression have been added in the Results section, Variables excluded from the analysis: page 9, paragraph 2: Although expected from literature and from the results presented in figure 3, it was not a significant predictor for any of fatigue dimension and it was eventually excluded in the regression process.

and further discussed on page 11, paragraph 2:

Although according to MRC dyspnoea classification there were significant differences for Reduced Activities, General and Physical Fatigue, the regression analysis excluded dyspnoea score as a possible predictive variable of fatigue. Importantly, the cohort used in regression study differ from one used in MRC classification analysis and data from home-assessed most severe patients may have been more insightful.

Minor essential revisions:

1. On page 14 dimension is spelled incorrectly.

Page 14: The spelling of the word ‘dimension’ have been corrected

2. On page 14 directly before Conclusions there is discussion about the reason that logistic regression was chosen. This piece seems misplaced and might have a better fit in the Statistical Analysis section.

Page 14: The fragment of the Discussion about logistic regression has been moved to the Methods section, Statistical analysis.

3. On page 16 some abbreviation definitions are capitalized and some are not.

Page 16: All abbreviation definitions have been capitalised.
4. **Figure 2 information is repeated in Table 1. You may not need Figure 2.**

   Figure 2 has been deleted.

5. **It would be helpful to the reader to have as many of the key variable mean/SD information in Table 1 as possible. Some of the information is in the text and some is in the Table. MRC information is missing.**

   Table 1 has been adjusted - all key variables including MRC score are presented in Table 1.