ORIGINAL RESEARCH LETTER

A systematic evaluation of the diagnostic criteria for COPD and exacerbations used in randomised controlled trials on the management of COPD exacerbations

To the Editor:

Acute exacerbations are largely responsible for the morbidity and mortality that characterise chronic obstructive pulmonary disease (COPD) [1]. Their optimal management still represents an urgent research priority [2]. Despite numerous randomised controlled trials (RCTs) evaluating the management of exacerbations, treatment has remained almost unchanged for over a decade and is only partly effective [1, 3]. Heterogeneity in the design of these trials has been an important obstacle, limiting the comparability of their findings. This heterogeneity has led recent Cochrane reviews to report limited confidence in the evidence supporting the most basic treatments used for exacerbations [4, 5].

Important sources of variability in the design of such trials include the selected outcome measures and the criteria used for diagnosing COPD and exacerbations. In a recent systematic review, we evaluated the outcomes measured and reported by 123 RCTs and 38 systematic reviews, published between 2006 and 2018 [6]. Here, we report on the diagnostic criteria for COPD and exacerbations that were used in these RCTs. Details on the methodology of this systematic review and the included RCTs have been published previously [6].

It is recommended that a COPD diagnosis should be based on a compatible clinical history and spirometric evidence of persistent airflow limitation during stable clinical disease [1]. This is, by definition, unattainable during an acute respiratory condition, when the specificity of spirometry is limited [7]. RCTs evaluating the management of exacerbations implement different methods to overcome this issue.

In our systematic review, described in detail previously [6], four (3%) of the included RCTs recruited patients during clinically stable disease, succeeding in acquiring a formal diagnosis of COPD prior to the exacerbation. A previous clinical diagnosis of COPD confirmed by spirometry was a prerequisite in 40 (33%) trials, a previous clinical diagnosis alone was acceptable in 23% of the studies and a typical history of chronic bronchitis at the time of recruitment was accepted in 24%. Finally, the diagnostic criteria for COPD were not reported or were unclear in 18% of the included studies. In order to confirm the diagnosis of COPD, several studies excluded patients with a diagnosis of asthma and/or atopy (19%), bronchiectasis (11%) or any other known respiratory diseases (6%).

In the absence of accurate biomarkers, the diagnosis of a COPD exacerbations is still based on clinical presentation. However, the clinical characteristics of COPD exacerbations are non-specific and can result from many other acute cardiorespiratory diseases. Different diagnostic criteria have been proposed [1, 8], which are more or less stringent and classify acute respiratory events differently.

The criteria proposed by Anthonisen *et al.* [8], which require an acute deterioration of at least two symptoms among sputum volume, sputum purulence and breathlessness, were most frequently used in the

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evaluated trials (24%), followed by those adopted by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (13%). GOLD defines exacerbation as an acute sustained deterioration of the patients' condition that is beyond the normal day-to-day variation and necessitates the administration of additional medications [1]. Three other trials (2%) used modified Anthonisen criteria, which required the presence of either two of the previously mentioned symptoms (major symptoms), or at least one major and one minor symptom, which included cough, wheeze, nasal discharge, sore throat or pyrexia [9]. Other combinations of specific symptoms (including any of the previously mentioned symptoms, tachypnoea or tachycardia) and biomarkers (parameters of the arterial blood gases, white cell count, neutrophil count or C-reactive protein) were considered as diagnostic in 23% of the trials, while 38% did not describe specific diagnostic criteria but mostly required a diagnosis by a clinician. Almost half of the trials (46%) recruited only hospitalised (severe) exacerbations. Reporting of the diagnostic criteria was poor in these studies, likely because a hospital diagnosis of COPD exacerbation *per se* is considered more accurate.

A number of studies specifically mentioned the exclusion of COPD mimics, such as pneumonia (33%), acute heart failure (19%), pneumothorax (3%) or pulmonary embolism (2%). To eliminate acute decompensation of left ventricular failure, some studies excluded patients with pre-existing cardiac failure, while others excluded presentations which were considered likely to represent decompensated cardiac failure by a senior physician. However, the acquisition of an echocardiogram or a computed tomography-pulmonary angiography to exclude mimics at presentation was not described in any of the trials. Finally, 22% of the studies only recruited patients who were symptomatic for at least 24–72 h and/or for a maximum of 10–14 days before presentation, as the probability of exacerbation mimics is considered to be increased in shorter or longer periods of symptoms, respectively.

Overall, diagnostic criteria for COPD and COPD exacerbations varied significantly across the included trials. Importantly, the diagnostic criteria were poorly described in many trials. These are problematic, as it has been demonstrated that the choice of different diagnostic criteria can significantly affect trial outcomes [3]. Thus, standardised diagnostic criteria should be used and clearly reported in such trials.

For the diagnosis of COPD, more stringent diagnostic criteria, requiring at least a previous clinical diagnosis of COPD, confirmed by post-bronchodilator spirometry during clinically stable disease may be more appropriate for efficacy trials, that require a more homogenous study sample. Effectiveness trials, which must reflect real-life, could adopt more pragmatic criteria, such as a previous clinical diagnosis, a history of chronic bronchitis or the presence of radiographic signs of emphysema, in a patient exposed to risk factors, such as cigarette smoking. We believe all participants of such trials should complete spirometry subsequently during clinically stable state. In addition, planned sensitivity analyses should include an analysis consisting solely of participants with prospective spirometric confirmation of COPD diagnosis. While recruitment during clinically stable disease would allow a formal diagnosis of COPD prior to the exacerbation, it is limited by the resulting substantial increase in the costs and follow-up period, as well as by the unavoidable selection of patients with frequent exacerbations.

For the diagnosis of exacerbations, the GOLD criteria have poor specificity and for this reason many trials adopted the Anthonisen criteria, which are more specific [9]. However, these were developed to identify infective exacerbations [9] and lack sensitivity to non-infective exacerbations, which are not characterised by increased sputum volume or purulence. The previously described modified Anthonisen criteria, which also include cough, wheeze, nasal discharge, sore throat and pyrexia, were developed to address this concern [10].

The list of COPD exacerbation mimics is sizable and should be actively sought in COPD exacerbation trials. Thorough clinical history and examination should be complemented by a chest radiograph, although this may not be possible in community recruitment. The role of cardiopulmonary ultrasound should also be explored. As described, symptom duration emerges as an important discriminatory parameter, since short periods of symptoms may represent a day-to-day variability in the symptoms of stable COPD [1]. However, this is not always practical (*e.g.* when trialling new ways of early reduction of inflammation). Similarly, the probability of having an exacerbation mimic is increased in patients who have been symptomatic for a long period before presentation (>10–14 days).

A critical issue that was only indirectly addressed by a small number of trials is the heterogeneity in the aetiology, underlying mechanisms, outcomes and response to treatment of exacerbations. Distinct acute disease entities that affect patients with COPD, such as bacterial infections, viral infections or events triggered by enhanced eosinophilic inflammation [10, 11], are currently grouped under a single umbrella term. However, it is not clear if this is appropriate, especially for the purposes of interventional clinical studies. It is anticipated that exacerbations respond differently to treatments, according to their aetiology. For example, only exacerbations triggered by bacteria would respond to antibiotics [10].

In conclusion, our review highlights the need for more standardised diagnostic criteria in trials of this frequent and often serious condition: a condition in need of a significantly improved evidence-base.

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