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Strategies to relieve dyspnoea in patients with advanced chronic respiratory diseases. A narrative review. Authors' reply

''I speak not to disprove what Brutus spoke, But here I am to speak what I do know'' .[1]

We thank Grogono et al.[2] for their interest in our review on management of dyspnoea in patients with **advanced** respiratory diseases.[3] Breathlessness requires much more attention by clinicians and researchers, as a major health problem around the world for millions of people[4] and their letter may contribute to the discussion.

Inhaled furosemide. Grogono et al.[2] give more details of their study in normal volunteers [5] as well as of other studies. We fully agree with their conclusion that *''**More** research with inhaled furosemide is justified''*. That's why in our review we concluded that *''based on available data, its (nebulised furosemide. . .) use for the routine management of dyspnoea in **terminal** patients is still either controversial or not indicated.''* Indeed we are unaware of any guideline recommending the use of inhaled furosemide in patients with **advanced** respiratory diseases.

Opioids. Practitioners and researchers have paid greater attention to management of pain than dyspnoea, and patients with **end- stage** respiratory diseases are less likely to undergo palliative care than patients with cancer.[6-8] The controversy on the use of opioids in respiratory diseases is long standing, and we *don't disprove what anyone spoke, we just speak what we do know*. Evidence based international guidelines recommend the use of opioids in *appropriate* doses, *formulations and schedules of administration* in patients with **advanced** chronic respiratory diseases,[9,10] but we understand authors' concern about potential long-term adverse effects, lack of effectiveness or risk of addiction. However, we described evidence based management of patients with **advanced** or **end-stage** respiratory diseases with poor short-term prognosis and life expectancy which would be probably not long enough to develop such potential long-term side effects.

Nobody denies that respiratory depression is a predictable adverse effect from a significant opioid *overdose*, while we need further clinical trials to better individualize treatment. Grogono et al.[2] blame us for ignoring the *''opioid crisis''* quoting a paper [11] on ''Opioid *Overdose*'' induced by illegal use or pain killers and not including *even once* the words *''**dyspnea**''* or breathlessness. *Overdose* in medicine means malpractice and this is not the case of guidelines. Illegal use or painkillers do not refer to the issue of our review,[3] As a matter of fact our review[3] underlined the *''need to be aware of and treat adverse effects''* while suggesting a therapeutical escalation exploiting all available pharmacological and non pharmacological tools described in the review.

Finally nobody portrayed *''those who harbour legitimate concerns about opioid safety as human rights violators''*, but we do think that avoiding *all* unpleasant and distressful symptoms, not only pain, in **terminal** conditions **IS** a human right. Whoever has treated or even only seen an **end-stage** dyspnoeic patient with pulmonary fibrosis asking for help, knows what we are talking about.

In conclusion Grogono et al.[2] criticize us for lack of *''full, accurate and balanced critical appraisal of the evidence''* just because they disagree with some of our evidence based ideas (or what they attribute to us) but we could not agree more with their recommendation. In our (unfortunately. . .) long life as researchers and clinicians we have always applied that principle, as is the case of this review,[3] however in all scientific controversies with our peers we have

always tried to rebut (rightly or wrongly) only what they truly meant.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Relationship between dyspnea/oxygen saturation and leg discomfort/6-minute walking distance in patients with COPD participating in pulmonary rehabilitation

Dear Editor,

Chronic and progressive dyspnea, the most characteristic symptom of chronic obstructive pulmonary disease (COPD), is often associated with physical activity reduction, not only because of the symptom itself but also because of the anticipation of discomfort caused by physical exertion.[1,2] Fatigue is also one of the main symptoms, described as the second most prevalent.[1,3] Therefore, relief of these symptoms is one of the primary goals in the management of patients with COPD.[2]

It is known that FEV_1 is not useful in predicting dyspnea and some studies have evaluated the relationship between dyspnea and dynamic hyperinflation.[1,4] Similarly, despite exercise-induced oxygen desaturation being observed in patients with COPD, mostly in those with more severe disease and with predominant emphysema phenotype, the underlying mechanism remains poorly understood.[5] Also, limb muscle dysfunction may play an important role in exercise limitation.[3]

As far as we know, no previous study has evaluated the relationship between dyspnea and oxygen saturation (SpO_2), nor between leg discomfort and distance walked.

The aims of this study were to investigate the association between dyspnea and SpO_2, and between leg discomfort and distance walked in the 6-minute walk test (6MWT), as well as the impact of Pulmonary Rehabilitation (PR) program on these variables.

This was a longitudinal retrospective study of patients with COPD who completed an outpatient PR program during 2016 at Pulmonology Department of Centro Hospitalar Universitário Lisboa Norte, Portugal. Subjects attended a multicomponent PR program with patient-tailored therapies, 8–16 weeks long. Those with ambulatory oxygen supplementation maintained it during the 6MWT and exercise training.

At the beginning and at the end of PR program, all patients underwent 6MWT. The variables analyzed were the degree of dyspnea and leg discomfort at the end of each 6MWT according to Modified Borg Scale, minimum SpO_2 observed by pulse oximeter and distance walked during the test.

Using software SPSS®, Wilcoxon or Studentś T-test were carried out, as appropriate, for comparison of variables at the beginning and at the end of the program. Associations