Finally, two bronchodilators are (or should theoretically be) more expensive than one. If that was the case, the cost-benefit ratio of dual therapy should be carefully considered, although we acknowledge that the organisation of different health-care systems around the world and their policy for reimbursement vary widely.

In conclusion, dual therapy is not synonymous with maximal bronchodilation, and the benefits of eventually achieving the latter need to be carefully investigated. Likewise, because of its potential implications for clinical practice (eg, dual therapy as a starting therapeutic step in all or some patients with COPD), research into this important subject is clearly warranted.

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Fatigue in COPD: an important yet ignored symptom


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Breathlessness, cough, and sputum production are cardinal symptoms of patients with chronic obstructive pulmonary disease (COPD). These respiratory symptoms are routinely assessed to monitor disease stability and also as outcomes of the efficacy of COPD-specific pharmacological therapies. Fatigue, however, is often ignored in clinical practice and research. Patients describe the sensation of fatigue as a general feeling of tiredness and being drained of energy, and it is associated with frustration, depression, and concentration problems.[1,2] Fatigue prevents patients with COPD from doing regular (instrumental) activities of daily life,[3] and is present in 50–70% of patients with COPD.[4]

Multiple factors might play a role in causing or maintaining moderate to severe fatigue in patients with COPD (figure). The amount of airflow limitation is poorly associated with fatigue, and optimal pulmonary pharmacological therapy does not seem to prevent deterioration of fatigue over time.[4] These findings suggest that COPD might not be the primary cause of fatigue. The experience of fatigue is a highly subjective experience and could be related to the amount of breathlessness experienced by the patient.[5] Moreover, COPD exacerbations (particularly those resulting in admission to hospital) were found to be important, precipitating factors of moderate to severe fatigue in patients with COPD.[5] In addition to increased breathlessness, many patients report low energy as one of the foremost sensations associated with a COPD exacerbation.[6] The infection itself might enhance fatigue. Additionally, low-grade systemic inflammation could flare up, common medical comorbidities might occur or intensify, and physical activity levels could decrease further during exacerbations and only partially recover. The extent to which these transient changes explain worsening of fatigue in patients with COPD remains to be elucidated. Moreover, the expected diurnal variation of fatigue and the most intense fatigue experienced before, during and after an exacerbation-related hospital admission remains unknown.

It seems reasonable to postulate that physical, psychological, behavioural and systemic factors might perpetuate moderate to severe fatigue in patients with

clinically-stable COPD. Indeed, fatigue is associated with worse health status, dysfunctional illness beliefs, focus on bodily sensations, worse mood status, exercise intolerance, poor sleep quality, and reduced physical activity levels, irrespective of the degree of airflow limitation.[3–5,7–9] Moreover, medical comorbidities, such as anaemia, hyperglycaemia, myocardial infarction, depressive symptoms, and obstructive sleep apnoea syndrome are common in patients with clinically-stable COPD, and they are all known to prolong fatigue. Nevertheless, the abovementioned factors have never been assessed concurrently in patients with COPD. In particular, the possible association between fatigue and medical comorbidities is poorly studied.[10] Therefore, the most important precipitating and perpetuating factors of fatigue in patients with COPD remain unknown.

With increasing insight into the precipitating and perpetuating factors of moderate to severe fatigue, health-care professionals will be able to identify individual or combinations of therapies that are needed to reduce fatigue in patients with COPD. Common medical comorbidities, if present, need to be treated adequately. Moreover, the prevention or an early intervention for COPD exacerbations is expected to reduce fatigue. This hypothesis has not been tested empirically yet. We do know, however, that a 10-week comprehensive, multidisciplinary pulmonary rehabilitation programme, with a specific focus on exercise training and cognitive behavioural therapy, significantly reduces fatigue.[11] Interestingly, clinically relevant improvements in fatigue following pulmonary rehabilitation were present in only 49% of the patients studied.[11] However, it remains unclear which components of a comprehensive pulmonary rehabilitation programme reduce fatigue. This knowledge will help to develop more fatigue-specific interventions.

To better understand the burden of moderate to severe fatigue and to assess the efficacy of specific therapies, simple validated questionnaires assessing fatigue need to be introduced in clinical practice.[12] These questionnaires will empower patients with COPD to discuss their sensations of moderate to severe fatigue with health-care professionals, which will provide insight into the fatigue experienced by patients during a previous period—eg, a week. However, it is difficult to capture diurnal variation of fatigue or the most intense fatigue experienced in questionnaires; they do not give information on the diurnal variation of fatigue or the most intense fatigue experienced. Indeed, fatigue is at least partly dependent on context and environment. Therefore, ecological momentary assessment is an interesting option to repeatedly assess fatigue in a patient's natural environment using digital data capturing. Indeed, patients are asked to report their fatigue on an electronic device (eg, smartphone, tablet) at random moments throughout the day.[13]

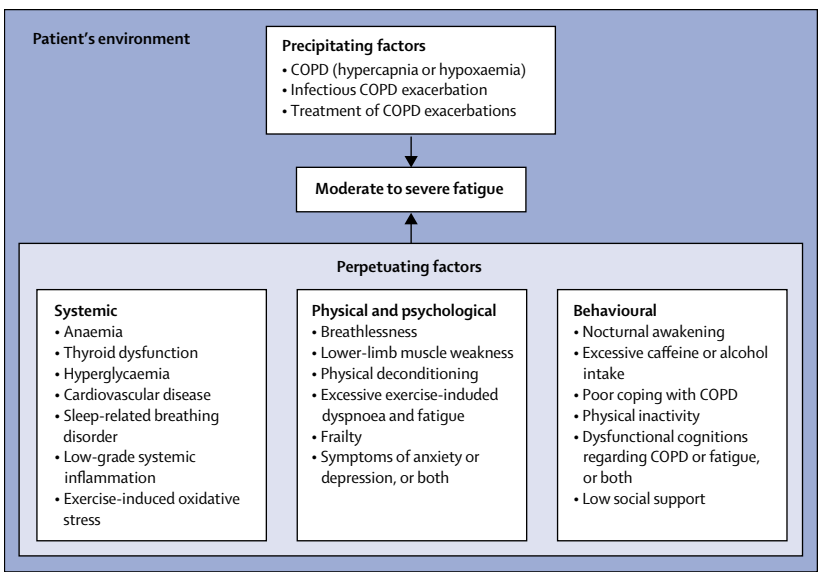

***Figure*: Possible precipitating and perpetuating factors of moderate to severe fatigue in the environment of a patient with COPD**

Fatigue is an ignored symptom in patients with COPD, yet, it is highly prevalent and incapacitating, and, in turn, affects societal participation and increases the burden of disease. Hence, patients with COPD need to be routinely questioned about their fatigue and research focusing on moderate to severe fatigue and its treatment needs to be intensified. The following factors need to be answered in the coming years: whether the physical, psychological, behavioural, and systemic factors precipitate or perpetuate fatigue in patients with COPD when studied concurrently; what is the diurnal variation of fatigue in patients with COPD before, during, and after an exacerbation-related hospital admission; how we can tailor a combination of therapies to reduce fatigue in individual patients with COPD; and whether a reduction in COPD exacerbations also results in a reduction in fatigue?

Research groups are now studying fatigue in patients with COPD, including the effects of cognitive behavioural therapy, lifestyle physical activity coaching, and providing L-carnitine supplements in combination with weekly

health coaching. The precipitating and perpetuating factors of moderate to severe fatigue in patients with COPD (physical, psychological, behavioural, and systemic factors (figure) are also being explored by the *FAntasTIGUE* consortium. The results of this research will hopefully provide further guidance for tailored interventions and help to lessen the effect of this debilitating symptom of COPD.

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Clinical trial research in focus: improving drug development and trial design in pulmonary arterial hypertension


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Over the past 20 years, more than ten vasoactive drugs have been developed and commercialised for the management of pulmonary arterial hypertension (PAH). As per initial regulatory requirements, early clinical trials were typically of short-term duration, comparing the effects of PAH-targeted therapies versus placebo, and using exercise tolerance as the primary endpoint. PAH study design has progressively shifted to longer-term, event-driven trials comparing combination therapy with monotherapy. Meta-analyses showed that monotherapy and combination therapy significantly reduced short-term mortality[1] and clinical worsening[2] compared with placebo and monotherapy, respectively. Despite these accomplishments, most patients continue to have poor quality of life, and long-term prognosis remains poor. Unfortunately, PAH combines the challenges inherent to treating a rare and devastating disease in which the knowledge of its complex molecular biology is in advance of available therapies. Innovative strategies to identify and effectively translate promising drugs to the clinical arena are thus warranted.

Accurate identification of therapeutic targets to be tested is central to this approach. Preclinical studies have provided new insights into the molecular and cellular pathways involved in PAH, and have played a crucial role in drug development. Similar to virtually all multifactorial disorders, however, current animal models do not encompass the features typical of human PAH,