



Limitations of a 6-min walk test to assess the efficacy of menthol for breathlessness

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To the Editor:

Walking is a vital component of physical activity in patients with chronic obstructive pulmonary disease (COPD). Exertional multidimensional breathlessness in daily life can reduce walking speed and time in patients with established COPD [1]. Improvement in breathlessness beyond a minimal clinically significant difference brought about by pulmonary rehabilitation, pharmaceutical bronchodilators and opioids has been reported [2–4]. However, despite guideline-directed disease-specific therapy, some patients with COPD experience residual breathlessness. Therefore, the application of a novel symptom-based treatment that is widely available will benefit patients with long-term breathlessness.

L-menthol is attracting attention as a potential novel symptom-based treatment for breathlessness in patients with COPD. The use of L-menthol for breathlessness in healthy volunteers dates back to a 1990 report by NISHINO *et al.* [5]. L-menthol, compared to control, decreased breathlessness induced by inspiratory loading [5]. Subsequently, in 2002, the transient receptor potential melastatin 8 gene (*TRPM8*) was cloned and reported to have the potential for activation by not only cold stimuli but also by a cooling agent, menthol [6]. Respiratory peripheral afferent input from the stimulation of TRPM8 channels on the trigeminal and the vagal neurons plays a key role in monitoring airway flow and in generating a cooling sensation in the upper airway. In 2017, we reported distinct evidence that the cooling sensation evoked by L-menthol, a TRPM8 agonist, alleviates breathlessness induced by constant-load cycling exercise and fixed inspiratory flow-resistive loaded breathing in healthy volunteers [7]. Moreover, in a clinical randomised controlled trial in older adults with and without COPD, we demonstrated that the cognitive illusion of inspiratory airway flow due to olfactory stimulation by L-menthol alleviated sensory and affective dimensions of breathlessness during inspiratory resistive breathing without a corresponding change in ventilation, breathing pattern or inspiratory neural drive assessed by surface electromyogram of the parasternal intercostal muscles [8]. Thus, the cognitive illusion of inspiratory flow *via* olfactory stimulation by L-menthol may represent an attractive option for alleviating breathlessness [8].

The physical activity and 6-min walking tasks performed at the patient's self-imposed intensity of effort are unable to unify the exercise stimulus causing breathlessness in the intervention and control arms. For this reason, to explore the possibility of using L-menthol to alleviate breathlessness during daily physical activities in patients with COPD, it is necessary to investigate the effect of L-menthol on breathlessness during standardised exercise stimuli. In addition, when examining the impact of any intervention on exertional breathlessness, the same exercise or ventilatory load should be used consistently in the intervention and placebo conditions. On these bases, the neural inspiratory drive, tidal volume and the frequency of breathing can be altered by placebo or active conditions, which require careful monitoring. However, the 6-min walk test is a form of field walking exercise in which the patient self-paces and does not provide a direct measure of the breathlessness response (or change in breathlessness response). Therefore, it has been recognised that the 6-min walk test should not be used as a measure of exertional breathlessness in clinical practice and research [9–11].

We recently read the article by PRIEUR *et al.* [12] published in *ERJ Open Research*. We would like to thank them for their investigation on the effect of menthol-containing chewing gum on breathlessness during real-world exercise tasks using the 6-min walk test. However, there are some questions that may benefit readers.



Shareable abstract (@ERSpublications)

L-Menthol is a novel treatment option for breathlessness in patients with COPD. However, the clinical application of menthol for the treatment of exertional breathlessness in these patients warrants further research. <https://bit.ly/3D6rLiJ>

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First, they reported that menthol reduced breathlessness by at least 1 point in 21 participants (33%) [12] and a positive effect on exercise tolerance was observed in 40 participants (63%) [12]. We request the details of the respiratory rate, inspiratory volume and oxygen saturation following the 6-min walk test in the 40 participants who showed improvement in their 6-min walk distance with menthol and the 23 participants who did not. Although assessing the intensity of breathlessness at the end of a 6-min walk test fails to determine the effect of menthol on breathlessness upon exertion, this would provide essential insights into whether the participants in the menthol and placebo conditions had comparable breathing conditions.

Second, there are two main forms of menthol, L-menthol and D-menthol, and the efficacy of the L form of menthol in breathlessness has been previously reported [3–5]. However, the type or the amount of menthol used in the authors' study [12] was unclear, which prevents further clinical application. Moreover, it is unclear whether the given gum was retained in the mouth during the 6-min walk test, as the study only reports them chewing it before. Therefore, we request information on whether the gum was also retained in the mouth during the exertion and details of the menthol compounds contained in the gum be provided.

Finally, although TRPM8 is not a so-called olfactory receptor, L-menthol can stimulate the olfactory and trigeminal nerves, and these nerves should be maintained to have an effect of L-menthol. However, the authors did not exclude patients with COPD with an impaired sense of smell. The lack of this screening is likely to inhibit testing of the efficacy of menthol and placebo, especially as patients with COPD are known to possess nasal symptoms [13].

L-menthol is highly accessible and versatile. Different methods of administering menthols such as crystal nasal inhalation [5], mouth swishing of diluted solutions [14], chewing gum [12] and olfactory stimulation [7, 8, 15] exist, but further research is needed to determine which methods are safe and effective, and in what dosages. Moreover, the clinical application of menthol for the treatment of breathlessness on exertion in patients with chronic respiratory diseases requires further research.

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