Palliative treatment of chronic breathlessness syndrome: the need for P5 medicine

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To the editor,

Breathlessness is the most frequently reported symptom by patients with advanced chronic lung disease or chronic heart failure and has widespread consequences.[1] Despite optimal treatment for the underlying disease, disabling breathlessness persists for many—recently named chronic breathlessness syndrome.[2] Patients, and their families, may live with chronic breathlessness for years, with serious functional and social limitations, care dependency and anxiety.[3] Clinical practice guidelines and policy statements now highlight pharmacological and non-pharmacological interventions for the palliative management of breathlessness as a cornerstone of care.[4 5] Despite this, many clinicians still feel ill-equipped and under-resourced to manage breathlessness, which remains a neglected symptom.[1 6]

Although the evidence base for breathlessness interventions is growing, important questions concerning optimal palliative management of breathlessness remain.[7] Studies of opioids are mostly small and of cross-over design. The most recent Cochrane review[8] found a smaller effect size and lower precision than other authors, although a repeat analysis[9] of the same studies accounting for the cross-over design of most showed a larger effect size with improved precision and benefit consistent with a clinically relevant improvement.[10] Safety concerns appear unfounded with oral low-dose opioid. Indeed, national cohorts of oxygen-dependent COPD and advanced interstitial lung disease found no association with excess hospital admission or mortality.[11 12] Another very large cohort of people with COPD showed a statistically significant, small absolute excess mortality but data regarding reason for prescribing (eg, pain or breathlessness) was not available making clinical interpretation difficult.[13] A systematic review found no evidence for clinically relevant respiratory adverse effects.[14]

In this issue, Currow and colleagues[15] describe the results of the first, large, parallel group trial studying efficacy and safety of 1 week's treatment with daily 20 mg oral sustained-release morphine compared with placebo for chronic breathlessness. They recruited 284 participants in 14 inpatient and outpatient cardiorespiratory and palliative care services in Australia. In contrast to the earlier positive results, they found no differences in the primary (breathlessness 'now') or secondary breathlessness scores ('worst/past 24 hours'; 'average/past 24 hours'; 'unpleasantness') between the study arms after 1 week of treatment. Health-related quality of life was comparable between groups. Of note, there was no between group statistical difference in adverse events, although constipation, nausea, fatigue and study-drug withdrawal were higher in the intervention group. Respiratory depression was not seen.

This well-conducted trial adds significantly to the available knowledge concerning morphine for breathlessness. It confirmed that low-dose morphine is well tolerated in this population, but raises the question of why they did not confirm previous positive findings. The authors discuss two limitations which might have contributed to the lack of effect. First, Currow *et al*[15] screened 1141 people for their study and managed to include 167 participants with modified Medical Research Council (mMRC) breathlessness grade 3 or 4. The eligibility criteria were expanded during the study to include people with mMRC 2 breathlessness in order to achieve their required sample size. An individual pooled data analysis of opioid trials showed that patients with less severe breathlessness were less likely to benefit[16] and it is notable that this trial's subgroup analysis (baseline mMRC 3 or 4), insufficiently powered to discard the null hypothesis, showed a benefit trend for 'worst breathlessness' and unpleasantness measures of breathlessness. Second, the ethics committee required that participants in both groups were allowed oral morphine solution as rescue medication. The placebo group used more rescue morphine, although both groups used low dosages and the difference was small. Nevertheless, this may have contributed to the lack of effect.

So, how to go from here? Should we put aside previous laboratory and clinical study evidence and conclude that the currently recommended pharmacological palliation of breathlessness, opioids, is ineffective? We argue not, but we do need to rethink how we assess, treat and study breathlessness in palliative care.

First, the bedrock of palliative breathlessness management remains non-pharmacological. This is prioritised in clinical recommendations such as the breathlessness 'ladder'[5] where opioids are reserved for those with persistent severe breathlessness despite non-pharmacological approaches in keeping with known predictors of opioid benefit.[16] Given the multifactorial genesis of breathlessness and its multicomponent complex management, distinguishing additional benefit from opioids is challenging in those where the relative contribution to benefit may be less. Therefore, opioid studies should exclude people with less severe breathlessness, and other interventions received should be documented, not only to prevent dilution of benefit, but to reflect the likely clinical context for use.

Second, therefore, we need to consider carefully how best to define such a study population. As Currow and colleagues correctly point out, mMRC assesses functional limitations of breathlessness, rather than its intensity, and has a ceiling effect in people with advanced disease.[17] Future clinical and laboratory studies are needed to further improve our understanding of patients most likely to respond to opioids. For example, recent functional MRI evidence suggests that depression may attenuate breathlessness benefit from opioids.[18]

Third, we need to rethink how we best measure patient-relevant breathlessness outcomes to evaluate the effect of interventions for chronic breathlessness. A unidimensional measure is unlikely to reflect full impact during daily life. The integral relationship between breathlessness and physical activity—with its own impact on function and quality of life—brings a further challenge.[19] Effective palliation will allow patients to be more physically active while experiencing the same intensity of breathlessness. The lack

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of physical activity measures in Currow *et al* does not allow us to interpret their findings in this light. Other candidates for meaningful outcome measurement should also be explored such as Ecological Momentary Assessment (EMA[20]) or Goal Attainment Scaling (GAS[21]). EMA involves repeated measurements of the patient's symptoms (such as breathlessness), behaviour and context in real time. Combined with assessment of physical activity, this might allow a more 'real-life' assessment of the effect of palliative treatments on breathlessness. GAS allows patients to set personalised rehabilitative goals.[21]

Meanwhile, chronic breathlessness remains burdensome for millions of patients globally. Attention for P4 medicine (predictive, preventive, personalised and incorporating patient participation) in chronic lung diseases such as COPD is increasing.[22] For effective treatment of such a complex syndrome as chronic breathlessness syndrome, we need P5 medicine (palliative, predictive, preventive, personalised and participatory): multicomponent *palliative* interventions which can be selected and applied based on a *prediction* of a beneficial response; breathlessness assessment and palliative interventions which can *prevent* further suffering; personalised palliative interventions tailored to individual needs and preferences; and involving patients as active partners in these palliative interventions which allow patients to *participate* in all their desired aspects of daily life.

Currow and colleagues are to be congratulated in completing a challenging trial. The research community must build on such work, incorporating key lessons, to develop the evidence base to inform management for people living with this debilitating and neglected syndrome.

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