

## Evidence-based intervention for chronic refractory breathlessness:

practical therapies that make a difference

### Clinical Question

What can the primary care practitioner offer patients with chronic breathlessness at rest or on minimal exertion which is refractory to treatments directed at the underlying cause of the symptom?

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### INTRODUCTION

Chronic breathlessness which is refractory to treatments for the underlying condition is a common symptom of frequently encountered conditions that present in primary care, including lung and heart disease, and cancer. Primary-care based chronic illness initiatives such as clinics for asthma or chronic obstructive pulmonary disease (COPD) and community heart nurse specialists play a vital role in optimising the management of the underlying condition(s), but for many people, especially in the later stages of the disease, breathlessness persists (chronic refractory breathlessness). Chronic refractory breathlessness is distressing for patients, their families and other caregivers, and for clinicians.

Clinically, chronic refractory breathlessness is a distinct entity, rather than simply a failure to treat the underlying condition(s). It requires a different approach than that required for acute breathlessness brought on, for example, by acute coronary syndrome, an acute exacerbation of COPD, or acute pneumonia.

### MANAGEMENT

The evidence base for the management of chronic refractory breathlessness has progressed in the past decade. Several therapies now have high quality evidence to support their use (sustained release opioids, non-pharmacological interventions) and there is high-quality evidence that oxygen should not be used for people with normal oxygen saturation. Some therapies require further research (such as benzodiazepines and antidepressants) (Box 1).

### Evaluation of chronic refractory breathlessness

A full assessment, given the multifactorial nature of breathlessness with physical, psychosocial, and spiritual contributions to the experience, is the crucial but often neglected first step. Identification of the contributing factors for any individual's

symptom is important to tailor interventions that, when combined, give incremental benefit. This includes a review to ensure that the patient is receiving optimal management of the underlying condition(s) and should occur at the same time that symptomatic treatment is initiated. All reversible factors should be identified and managed even where there appears to be a single dominant explanation for the symptom. A consecutive case series of 100 people with advanced cancer found that half had potentially reversible causes including untreated arrhythmias, bronchospasm, and anaemia.<sup>1</sup> People in this cohort had a median of five potentially modifiable causes for breathlessness.

### Non-pharmacological interventions

A systematic review and meta-analysis of data from randomised controlled clinical trials for the symptomatic relief of breathlessness confirms strong evidence in support of interventions that help to reverse deconditioning and encourage exercise, thus maximising the mechanical function of the chest wall and optimising skeletal muscle efficiency.<sup>2</sup> Breaking the cycle of deconditioning is an important element, confirmed by other trials of pulmonary rehabilitation and exercise. Tailoring the relevant non-pharmacological interventions to each patient's needs is still poorly defined in the literature but access to multidisciplinary team members such as a physiotherapist or occupational therapist with an interest in respiratory disorders is likely to be beneficial. Access to these therapists is not routine (nor indeed easily available) in the care of patients with breathlessness, and formal breathlessness services (as distinct from pulmonary rehabilitation services) are even rarer.

### Pharmacological interventions

There is level 1 evidence that regularly monitored, low dose, sustained-release morphine is effective and well tolerated

## Box 1. Evidence for interventions in chronic refractory breathlessness

### For benefit

*Strong level evidence:*

- Sustained release morphine

*Moderate level evidence*

- Walking aids
- Breathing training and activity pacing
- Exercise

*Insufficient evidence*

- Benzodiazepines

### Against benefit

*Strong level evidence*

- Oxygen
- Buspirone

for the treatment of chronic refractory breathlessness.<sup>3,4</sup> In a dose increment study ( $n=83$ ; mean age 75 years) and an embedded pharmacovigilance study ( $n=52$ ), which together collected more than 30 patient/years of data, 10 mg daily of sustained-release morphine was administered, and increased in non-responders by 10 mg daily each week to a maximum of 30 mg daily.<sup>5</sup> Of the two-thirds who benefited, over 90% had done so with a dose of 20 mg daily or less. There was no subsequent evidence of tachyphylaxis when people were followed for up to 22 months. There were no opioid-related hospital admissions in any of the trials that formally measured toxicity including respiratory depression, despite most participants having COPD.

### Therapies where evidence does not support current practice

Oxygen is widely used for the palliation of breathlessness even in people who are not significantly hypoxaemic. A meta-analysis of people with cancer<sup>6</sup> together with an adequately powered phase III double-blind,<sup>7</sup> randomised controlled trial demonstrated that there was no improvement in breathlessness from oxygen over and above the placebo arm of 'medical air' in people who did not qualify for long-term home oxygen. A separate meta-analysis explored the use of oxygen in people with COPD, similarly ineligible for long-term oxygen, that did show greater symptomatic benefit from oxygen compared with medical air.<sup>8</sup> However, the studies were small and were not designed to detect an improvement in breathlessness as their primary objective.

From the benefits of 'medical air' seen in people with chronic refractory breathlessness who are not hypoxaemic, airflow across the face/nasal mucosae seems to be an important mechanism in symptom reduction. There is emerging evidence to support the use of the handheld battery operated fan. Such simple measures can be safely and effectively used by patients or provided by those that care for them.

Benzodiazepines are commonly used for breathlessness, and there is an intuitive rationale for their use given the interplay with anxiety in worsening breathlessness for many people. However, a recent meta-analysis was unable to find evidence to support or refute their use in this setting; the quality of data available for the meta-analysis was universally poor. There is a need for a well-designed study to understand the role of benzodiazepines alone or in combination with regular, low-dose opioids. The potential for tolerance

early in treatment and dependence with prolonged administration should discourage their use until better evidence is available.

Buspirone, the anxiolytic drug, was not shown to improve breathlessness in a recently reported, well designed, adequately powered phase III study with 433 participants.

### CONCLUSION

Patients with a variety of underlying aetiologies suffer chronic refractory breathlessness that appears to be mediated through a common central nervous system pathway. It is likely that treatments that are effective in one patient population may be useful in other populations similarly affected, although confirmatory studies are needed.

Adequate assessment of potentially reversible causes (at the same time that symptomatic treatment is initiated), use of non-pharmacological interventions, and judicious use of regular low-dose opioids (with aperients) are strategies that in combination help to reduce the intensity of chronic breathlessness that is no longer responding to disease-modifying therapies. No single therapy is likely to eliminate such breathlessness but, in combination, there is an ability to reduce the burden of breathlessness.

As the evidence base progresses, it is important to make sure that these safe and effective therapies are available to patients with chronic refractory dyspnoea. Primary health care is the main health service contact for many of these patients. With its multiprofessional and holistic approach, primary care is ideally placed to address this symptom systematically.

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### Competing interests

The authors have declared no competing interests

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