

Managing breathlessness in advanced disease

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Breathlessness in advanced malignant and non-malignant disease is frequently chronic and refractory. It persists at rest and on minimal activity despite optimal management of the underlying disease process.

Concept of breathlessness

The terms dyspnoea ('difficult breathing'), breathlessness and shortness of breath are often used interchangeably. Breathlessness is the term most often used by patients. Other patient descriptors, such as air hunger, increased work of breathing, chest tightness and a feeling of suffocation, have been disappointing in identifying specific pathophysiologicals to allow targeted intervention. Temporal patterns of breathlessness, including continuous or episodic breathlessness, with or without apparent triggers, are a current topic of research¹ in the hope that such discrimination will inform future management choices.

Breathlessness is a symptom that can only be described and interpreted by the patient.² It should be considered as distinct from the traditionally observed physiological parameters that physicians use when assessing for respiratory compromise, such as respiratory rate, oxygen saturation and the use of accessory muscles.

[Breathlessness is] a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary, physiological and behavioural responses.

American Thoracic Society (1999)¹

Prevalence and impact

Breathlessness is common in patients with advanced life-threatening illnesses of all types. The prevalence reaches 90% in cancer, 95% in chronic obstructive pulmonary disease (COPD), 88% in cardiac failure, 80% in end-stage renal disease and 85% in advanced neurological disease.³ Both prevalence and intensity increase as death approaches.

Breathlessness causes significant suffering to patients and to carers, profoundly disrupting day-to-day functioning and causing social isolation. It can engender helplessness, be linked to thoughts of impending death and be a major trigger for hospital admission.

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Mechanism of refractory breathlessness

Unlike the normal 'physiological' feeling of being out of breath generated in health by physical exertion (eg climbing stairs at speed), the experience of breathlessness in advanced disease is more than a simple symptom, rather a complex set of interactions between physical, psychological and emotional factors that are further modulated by an individual's past experiences, expectations and fears for the future.

It is all too easy to underestimate the experience of breathlessness and the associated suffering. The sensation of breathlessness is generated when higher cortical centres perceive what the respiratory system can provide as inadequate or unsustainable to meet the body's requirements, and the patient may perceive a significant threat to survival (Fig 1).

Recent functional neuroimaging studies have shown that breathlessness, irrespective of cause or stimulus, activates distinct areas in the limbic system.⁴ This region is rich in opioid receptors and probably generates the conscious awareness of breathlessness and the associated sensation of unpleasantness.

Assessment

Breathlessness is a subjective symptom that cannot easily be quantified, and there is no commonly agreed assessment tool.⁵ Few parameters measured in pulmonary function laboratories

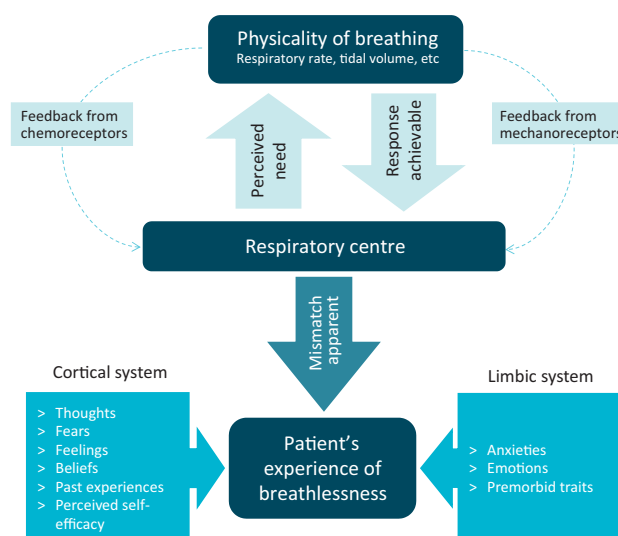


Fig 1. Mechanism of breathlessness in advanced disease.

are representative of real life, and they are too burdensome for use in patients with advanced disease states. The assessment of breathlessness should reflect patients' reporting of both severity and affective components.

When assessing any response to intervention, consideration must reflect patient-relevant outcomes. Success, therefore, may be a reduction in intensity of breathlessness, a reduction in psychological distress, an increase in activity levels or a reduction in hospital admissions.

In patients with advanced disease, there is little potential of returning to a non-breathless state. There may be a delay in the patient developing confidence in an intervention before achieving mastery of breathlessness and increased performance. Small objective increments (5.5 mm on a 100 mm visual analogue scale) can translate into meaningful improvement for patients.⁶

Treatment

Ensure that treatment for the underlying disease is optimised in the context of disease trajectory, performance status and patients' wishes. Patients with advanced cancer can develop

heart failure but respond to treatment with significant improvement in symptoms. Conversely, treating a pleural effusion will not benefit a dying patient. Potentially reversible causes of breathlessness include pulmonary embolus, infection, arrhythmia, anaemia and ascites.

Evidence base for non-pharmacological treatment

Two Cochrane reviews and four systematic reviews published since 2008⁷⁻⁹ have recommended non-pharmacological approaches for intractable breathlessness associated with advanced disease. These are summarised in Table 1.

Evidence base for pharmacological treatments

Opioids

Opioids are the mainstay of pharmacological intervention for breathlessness and multiple randomised controlled trials (RCTs) and systematic reviews^{11,12} have shown significant reductions in breathlessness with the use of oral or parenteral opioids in patients with advanced disease. Most studies have used morphine, but a class effect is assumed.

Table 1. Non-pharmacological interventions to manage breathlessness.

Intervention	Aim	Evidence
Pulmonary rehabilitation and exercise	Desensitises patient Reduces deconditioning Lowers ventilator demand and slows respiration	Strong for COPD Inconclusive for advanced malignancy or patients deteriorating systemically
NMES	Induces quadriceps contractions as an alternative to exercise	Strong for COPD Not readily available for most patient groups
Forward positioning	Fixes shoulder girdle Improves efficacy of accessory muscles	Limited, but patients with COPD develop this pattern naturally, which suggests a benefit
Walking aid	Allows forward leaning and decrease work of breathing during exercise Increases patient confidence	Moderate
Breathing retraining/'blow as you go' pursed-lip breathing	Promotes more efficient breathing pattern and improved gas transfer	Moderate Much variability across literature, which hampers comparison
Facial cooling/HHF/piped medical air	Interrupts signals from upper airway to brainstem respiratory centre	Strong for short term Mixed for long term HHF is safe and inexpensive
Acupuncture	Stimulation of endogenous beta-endorphin release	Limited published evidence Local experience suggests benefit
Anxiety-reducing interventions such as CBT	Addresses psychological and emotional components Promotes self-mastery and delays spiral of inactivity and deconditioning	Evidence for CBT in advanced COPD is limited but promising
Multi-professional breathlessness intervention clinic	Provides combination of non-pharmacological and pharmacological strategies Improves patient self-efficacy	Preliminary results from MRC's randomised controlled trial seem positive ¹⁰

CBT = cognitive behavioural therapy; COPD = chronic obstructive pulmonary disease; HHF = hand-held fan; MRC = Medical Research Council; NMES = neuromuscular electrical stimulation.

Opioids are proposed both to reduce the spontaneous respiratory motor response to hypercapnia and hypoxia and to modulate the central processing such that perceptual sensitivity to breathlessness is diminished.¹³ Important gaps remain in the knowledge base regarding variability in the degree of opioid responsiveness and tolerability between patients. Recent work suggests that younger patients and those who experience the greatest severity of breathlessness are most likely to benefit.

Fears around safety are common but unsubstantiated. Several studies have shown no evidence of significant opioid-induced respiratory depression or hastened death, such that their use is now recommended in advanced respiratory disease.¹⁴

Expert opinion regarding the initiation of opioids for breathlessness lies in two camps: commencement of long-acting morphine (10 mg daily)¹² vs more gradual titration using low-dose, short-acting morphine.¹⁵ Local practice

in our hospital favours the second approach, starting with low-dose, short-acting morphine (1–2 mg twice daily plus 1–2 mg as required) and with judicious weekly uptitration to the minimum effective dose that improves tolerability of breathlessness and limits opioid-related adverse effects. Side effects, especially constipation, should be anticipated and managed proactively. Recent studies looking at the longer term benefits and acceptability of low-dose opioids for patients with COPD are encouraging.¹⁵ For patients already established on opioids for pain, an increment of 25% above baseline is recommended.

Oxygen

Long-term oxygen therapy improves both survival and quality of life for patients with COPD with significant chronic hypoxia. Oxygen is often prescribed for palliation of breathlessness in the setting of other advanced disease, but the evidence base does not support this practice in the absence of hypoxia. A Cochrane review and a large RCT comparing oxygen and room air via nasal cannula showed no additional symptomatic benefit with oxygen over room air in non-hypoxic patients with malignant and non-malignant aetiologies.^{16–18} Movement of air across the face may be beneficial, and this can readily be achieved using a fan. Opioids have been found to be significantly better than oxygen in reducing breathlessness.¹³

Short-burst oxygen supplementation may prevent desaturation during exercise but may not relieve breathlessness. Careful assessment of symptomatic benefit on an individual basis is recommended.

Anxiolytics

Significant interplay between breathlessness and anxiety is often present, making it difficult for patients and clinicians to distinguish the primary source of distress.

Benzodiazepines are often used for breathlessness, but the evidence base is sparse. Recent reviews identified only a non-significant trend for cancer- and non-cancer-related breathlessness.¹⁹ Two more-recent RCTs support a modest benefit of midazolam, particularly in combination with morphine.²⁰

In practice, a therapeutic trial of low-dose benzodiazepine (lorazepam 0.5–1.0 mg sublingually as required) would be cautiously recommended when anxiety is prominent and breathlessness is not amenable to non-pharmacological interventions and opioids.

Antidepressants with anxiolytic properties, such as mirtazapine and citalopram, may have a role alongside non-pharmacological interventions (Box 1).

Conclusion

Breathlessness is the subjective experience of not being able to breathe comfortably. It is a common and distressing multi-dimensional symptom. An interdisciplinary approach that considers both non-pharmacological and pharmacological measures can substantially reduce its impact for patients (Fig 2). ■

Box 1. Breathlessness in the last days of life.

- > Pharmacological management predominates as death approaches
- > Consider:
 - oxygen only if hypoxic
 - converting to the subcutaneous route if already established on regular opioids
 - morphine sulphate (5–10 mg subcutaneously over 24 hours) if opioid naïve
 - midazolam (5–10 mg subcutaneously over 24 hours)
 - further titration to the lowest effective dose

Key points

Severity of breathlessness is unrelated to measurable parameters or disease status

No single intervention is likely to relieve refractory breathlessness; aim to change perception and experience of breathlessness

The most effective regimens for palliation of breathlessness include concurrent use of non-pharmacological and pharmacological interventions

Opioids can safely reduce the subjective sensation of intractable breathlessness

Oxygen may correct hypoxia, and movement of air palliates breathlessness

KEY WORDS: Breathlessness, multi-professional approach, opioids, subjective, symptom mastery ■



Fig 2. Management of breathlessness in advanced disease.

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