Symptom control and palliative care: management of breathlessness

Breathlessness remains a common and significant problem in palliative care. This article reviews the most commonly used interventions and discusses strategies to improve this symptom.

Breathlessness, or dyspnoea, remains a management challenge in symptom control, especially in advanced disease. At the end of life, poorly controlled dyspnoea can be distressing to patients, carers and health-care professionals. Traditionally, the use of certain drugs, particularly opioids, has been discouraged at it was considered that these may contribute to respiratory depression and hasten death. This article defines and determines the nature of breathlessness, discusses potentially reversible causes, explores mechanisms responsible for intractable breathlessness in advanced disease and details the management strategies commonly used for breathless patients.

Definition of breathlessness

Breathlessness is one of the most common symptoms in palliative care and can be present in advanced disease either from aetiologies where breathlessness may be prominent throughout the course of the disease (such as chronic obstructive pulmonary disease or heart failure) or simply as a result of disease progression (notably cancer or neuromuscular disorders). Up to 70% of all cancer patients describe some form of symptomatic breathlessness in the last 6 weeks of life (Reuben and Mor, 1986). Dyspnoea has been defined by the American Thoracic Society (1999) as:

> **'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'.**

The terms dyspnoea, breathlessness and shortness of breath are used interchangeably.

Breathlessness remains a subjective sensation that cannot easily be quantified by a single measure. Objective measures such as respiratory rate, blood oxygen saturation and arterial blood gas values are quoted as surrogates for breathlessness but do not actually measure dyspnoea. Patients can remain breathless despite normal oxygen saturation or respiratory rate, making objective improvements after therapy difficult to quantify in research terms. Numerical rating scales, verbal rating scales, visual analogue scales and the modified Borg scale remain the more commonly used methods of measurement in research, although there is no accepted gold standard or agreed timing of measurement (average score, worst score or current scores are most frequently adopted). Distress caused by breathlessness is another factor that can be measured in this fashion and can be important in patients with breathlessness at the end of life. Qualitative descriptions of breathlessness can vary between diagnoses, suggesting a number of potential mechanisms for breathlessness dependent on aetiology, although these descriptions do not seem to be consistent or robust enough to aid differential diagnosis (Wilcock et al, 2002).

Causes of breathlessness

Breathlessness in palliative care patients can be multifactorial and potentially reversible causes should be considered and treated if appropriate (*Table 1*). Individual

Table 1. Potentially reversible causes of breathlessness in palliative care patients

Pneumonia
Anaemia
Exacerbation of asthma
Pulmonary embolus
Cardiac failure
Exacerbation of chronic obstructive pulmonary disease
Pneumothorax
Arrhythmias
Lymphangitis carcinomatosis
Pleural or pericardial effusion
Cardiac ischaemia
Stentable airway obstruction
Ascites
Psychological or anxiety
Cachexia

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clinical judgment should include the need for further investigations to determine any reversible cause and the suitability of further treatment. Pneumonia and pulmonary embolus are two of the more common causes, but consideration must be given as to the benefits of therapy (e.g. antibiotics, anticoagulation) compared to the burdens of treatment in a frail population. Patients with disease processes that directly cause breathlessness such as asthma, chronic obstructive pulmonary disease or heart failure should continue on their disease-specific medication where tolerated and appropriate.

The pathophysiology of dyspnoea is poorly understood. The respiratory centre in the medulla and pons of the brain regulates respiratory function by coordinating the activity of respiratory muscles including the diaphragm (Manning and Schwarzstein, 1995; American Thoracic Society, 1999). It receives direct and indirect input from central and peripheral chemoreceptors, pulmonary stretch receptors and vagal afferents, peripheral mechanoreceptors and the cerebral cortex (Thomas and von Gunten, 2003). In dyspnoea, some or all of these inputs are altered, leading to the sensation of breathlessness. This may be a consequence of increased work of breathing, chemical imbalance (e.g. hypercapnoea) or neuromechanical dissociation between afferent inputs to the cerebral cortex and respiratory centres and the requirement for respiratory drive (Manning and Schwarzstein, 1995). In particular, it is now considered that a sensory–ventilation (afferent) mismatch occurs between the expected and perceived work of breathing, resulting in a drive to increase ventilation that may be perceived as breathlessness (American Thoracic Society, 1999; O'Donnell et al, 2007).

The causes of intractable breathlessness have been difficult to research and, as a result, there is no specific, evidence-based therapy developed to help relieve this symptom. Towards the end of life, treatment should be centred predominantly around the alleviation of such distressing or troublesome symptoms through reducing anxiety and improving perceived or actual airflow (see later). Therefore, in practice non-disease-specific treatment strategies are used. This may include the use of sedative medication to reduce anxiety and sensations of breathlessness if the patient becomes agitated or distressed by dyspnoea (Twycross and Wilcock, 2001).

General management

It is important to acknowledge the anxiety and fear caused by a perceived inability to breathe. The aims and expectations of management should be discussed with both patients and carers. Breathing retraining methods can give control over acquired dysfunctional breathing patterns and these should be used if the patient is able to participate. A Cochrane review of non-pharmacological interventions in patients with advanced disease (mostly chronic obstructive pulmonary disease) suggested evidence of benefit for particular interventions including chest wall vibration and neuro-electrical muscular stimulation, breathlessness training and walking aids if the patient is ambulant (Bausewein et al, 2008). Anxiety management and relaxation training programmes, often provided by physiotherapy or occupational therapy colleagues, may also be of benefit, as can some complementary therapies. Non-pharmacological interventions should always be considered before, or in addition to, pharmacological measures. Although not all centres will have access to these measures, all areas should have access to physiotherapy and occupational therapy and a multiprofessional team approach is recommended.

Correct posture can help both breathlessness (by reducing diaphragmatic splinting and assisting the accessory muscles of breathing) and retained secretions. In addition, continuous airflow across the area of the face supplied by the second and third branches of the trigeminal nerve has been shown to reduce the sensation of breathlessness (Booth et al, 2008) and for this reason every breathless patient should have access to a fan (hand held or free standing).

As death approaches, the appropriateness of a patient's regular medications should be reviewed. Factors that may exacerbate breathlessness should be identified and avoided where possible. For example, care should be given to the use of intravenous fluids, as fluid overload at the end of life can lead to distressing breathlessness and retained secretions (death rattle). This symptom can be particularly upsetting for carers and staff and can be difficult to alleviate with antisecretory agents (hyoscine butylbromide 20 mg subcutaneously, four times a day or glycopyrrolate 400 μg subcutaneously, four times a day) once established. The nature of breathlessness can change as death approaches, with development of periods of apnoea, rapid breathing or Cheyne–Stokes respiratory patterns. These may not be perceived as breathlessness by the patient as he/she becomes more comatosed, but the effect of these respiratory patterns on carers and relatives should be acknowledged.

Specific interventions for breathlessness

Opioids

Opioids are the mainstay of breathlessness management in palliative care. However, it is still unclear as to the mechanism of action of opioids in relieving dyspnoea and whether they exert a predominantly central or peripheral effect. A Cochrane review of the use of opioids in patients with intractable breathlessness of various aetiologies demonstrated a symptomatic benefit when opioids were delivered orally or parenterally, but not by nebulized therapy (Jennings et al, 2001). A total of 18 randomized double-blind controlled studies involving opioids for breathlessness were identified, of which nine involved parenteral or oral administration. Subsequent meta-analysis of these studies revealed a small but statistically significant symptomatic improvement. There was no difference in efficacy between oral and parenteral opioids,

however, and the oral route should be used where possible. More recently, Abernethy et al (2003) performed an adequately powered placebo-controlled randomized trial of oral opioids for intractable breathlessness in mainly chronic obstructive pulmonary disease patients who were opioid naive. Again, a small but significant improvement in subjective dyspnoea was observed with morphine sulphate modified-release 20 mg daily. Thirty-eight of the 48 patients completed the crossover study, with five withdrawals as a result of opioid side effects.

Further investigations involving the use of nebulized opioids are ongoing, but at present little evidence exists to recommend this method of opioid delivery. Interest in this method of delivery has persisted because of the ease of use of nebulized therapy and the localization of opioid receptors in the lungs (Zebraski et al, 2000). Two randomized controlled crossover trials involving a total of 31 patients with a cancer diagnosis have shown no statistically significant difference between nebulized and parenteral opioid therapy for breathlessness (involving morphine in one study and hydromorphone in the other) (Bruera et al, 2005; Charles et al, 2008). These studies used larger nebulized doses than had been used in studies previously, but the absence of any difference between methods of delivery cannot be concluded because of the small sample size in both studies.

What is clear from these symptom control studies is that opioids are safe to use when administered in appropriate doses. In particular they do not appear to cause significant respiratory depression when administered in small doses. The common side effects of opioid therapy (notably nausea and constipation) should be proactively managed by co-prescription of laxatives and anti-emetics on an 'as required' basis. There is little evidence to suggest that one opioid is superior to another or whether long-acting opioids are as beneficial as short-acting ones. Oral morphine sulphate solution (initially 5 mg by mouth, four times a day in an opioid-naive patient) is still the most commonly used oral drug in clinical practice because of its ease of administration, titration and availability in the UK. Some patients may find an as required dose useful to alleviate breathlessness, particularly before exertion. Doses can be titrated upward after 48 hours depending on efficacy and adverse events.

Conversion to long-acting opioids can be made once a stable dose level is reached. Some physicians consider that long-acting opioids can be used from the start of treatment, as is current practice in some centres for the alleviation of pain with opioids. Certainly, the Abernethy et al (2003) study suggests this can be the case, but some patients may prefer taking a shorter acting medication that gives a more rapid perceived symptom effect. No evidence-based guidance exists as to the appropriate dose of opioid for breathlessness if the patient is not opioid-naive, but it is suggested that an as required dose of 25% of the normal as required dose for pain would be appropriate (Allard et al, 1999).

Oxygen

Oxygen is commonly administered to patients who experience breathlessness and is often perceived by both patients and professionals to be beneficial. The administration of supplemental oxygen via face mask or nasal cannulae is a powerful visual indicator of medical intervention, but its use can often occur as the result of professionals' desire to be seen to do something active to try and alleviate a particularly distressing and often intractable symptom. In fact, intractable dyspnoea has been cited as the most common reason for prescription of oxygen by palliative care specialists and respiratory physicians (Abernethy et al, 2005). However, the therapeutic use of oxygen is more than a simple correction of reduced blood oxygen levels (Gallagher, 2003). Certainly, many more patients than those proven to be hypoxaemic perceive benefit from its use and blood oxygen levels do not correlate with subjective feelings of breathlessness (Thomas and von Gunten, 2003).

There is some evidence, albeit inconsistent, that both oxygen and air can reduce feelings of breathlessness in patients with malignant disease (Bruera et al, 1992; Booth et al, 2004). The proposed effect of sensory stimulation by blowing cool air on the face, distinct from placebo effect or increasing blood oxygen concentration, has already been discussed. The evidence for the use of oxygen in the management of breathlessness in palliative care patients is limited and mostly of a low quality; certainly, there are no large randomized controlled trials looking at the use of oxygen in this population. In a randomized, double-blind crossover study, Bruera et al (1992) found that supplemental oxygen did improve breathlessness in patients with cancer, although a later study did not support any additional benefit of oxygen as compared with air (Davis, 1999). Current evidence does not help professionals target patients who would specifically benefit from administration of either air flow therapy or supplemental oxygen.

An international, randomized, double-blind trial is currently being conducted in an attempt to determine the effects of supplemental oxygen therapy in palliative care. Early results from this study suggest that palliative care patients 'self-select' with regard to benefit from oxygen therapy, as continued use without a beneficial effect on symptoms is burdensome (Currow et al, 2007).

Heliox

Heliox is a gaseous mixture made up of 79% helium and 21% oxygen. It has been used in medicine for several decades, often where relief from upper airways obstruction has been required, as it allows patients to breathe more freely because it has a much lower density than both oxygen and air. A small trial of the use of Heliox 28 (28% oxygen, 72% helium) in breathless patients with lung cancer found significantly lower levels of breathlessness in

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those patients using heliox during a 6-minute walk test than those using either oxygen or medical air (Ahmedzai et al, 2004). However, evidence for the more widespread use of heliox in palliative care remains scarce and further research into its use and effects is required. Access to heliox can be limited, especially in community settings.

Benzodiazepines

A timeless conundrum in medicine is the nature of the relationship between anxiety and breathlessness. Certainly patients frequently report anxiety in association with sensations of breathlessness. Anxiety can sometimes exacerbate breathlessness but, equally, breathlessness can cause, heighten and perpetuate feelings of anxiety. Both are powerful emotional, psychological and physical sensations and can occur simultaneously, making it difficult for both patients and professionals to distinguish one from the other (Thomas and von Gunten, 2003). This adds to the challenges associated with managing a distressing and debilitating symptom cluster.

Benzodiazepines have frequently been prescribed in the management of breathlessness over the past three decades, but evidence for their effectiveness has been mixed (Sen et al, 1983; Greene et al, 1989). Certainly, benzodiazepines do not appear to be effective unless used in combination with other management strategies (Thomas and von Gunten, 2003).

The ability to distinguish between anxiety and breathlessness as a primary source of distress may be useful. Opioids have been used to manage breathlessness, as already discussed, and it may be clinically beneficial to determine whether opioids alone reduce symptoms, as their anxiolytic properties are not sustained through repeated use (Thomas and von Gunten, 2003). Thereafter, where anxiety is thought to be a major contributory factor in breathlessness, benzodiazepines may be an appropriate therapeutic option. Midazolam appears to be the most commonly used medication for sedation in patients with panic or distress in the terminal phases of illness in palliative care (Cowan and Walsh, 2001), but in specialist palliative care, sublingual lorazepam (e.g. 0.5–1 mg sublingual administration, as required) is often used because of its short duration of action (the sublingual route is not licensed, but is an accepted route of use in palliative care). Diazepam is also used by some clinicians to reduce anxiety, and associated breathlessness, but its use should be monitored because of its longer duration of action and potential side effects.

Inhalers and nebulizers

The possibility for delivery of opioids to the respiratory tract via nebulizer for the relief of breathlessness has already been mentioned. However, some low level studies and observational reports have suggested the use of nebulized furosemide, a loop diuretic, for symptom relief in palliative care patients (Stone et al, 1994; Shimoyama and Shimoyama, 2002; Kohara et al, 2003). It has been proposed that furosemide acts on the tissues of the lung to inhibit cough and reduce the effect of stimuli that cause bronchoconstriction (Ventresca et al, 1990), although this remains unclear and the mechanisms involved may not be so straightforward. However, Wilcock et al (2008) demonstrated no appreciable difference in benefit from the use of nebulized furosemide when compared to normal saline.

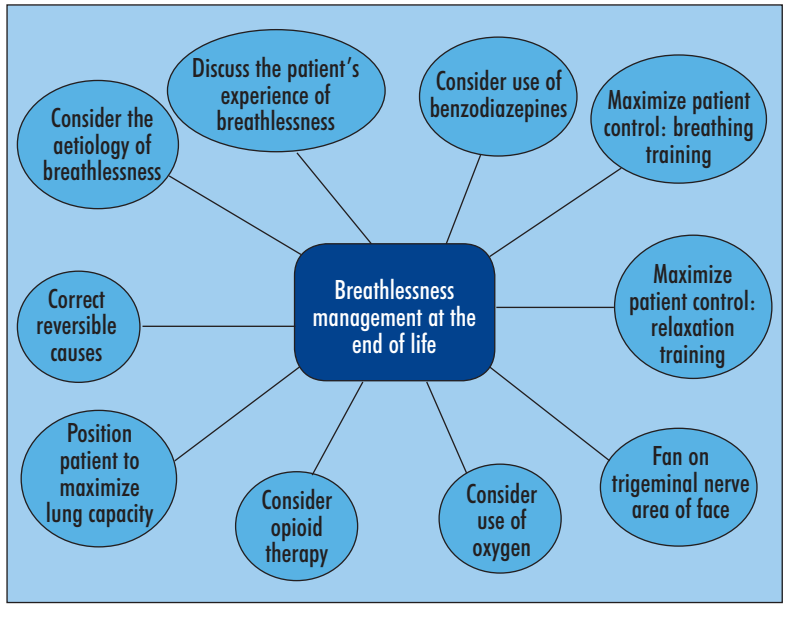
Cognitive-behavioural, anxiety-reduction and complementary interventions

As discussed, the experience of breathlessness is influenced by physical, psychological and emotional factors and, as such, non-pharmacological approaches to management have a role in the control of breathlessness. Structured approaches for patients involving education, self-management strategies and psychological support have been shown to be effective (Bredin et al, 1999). Anxiety-reduction training, often included as a component of breathlessness management programmes, uses a variety of different techniques to achieve a reduction in fear or panic, and subsequent reduction in breathlessness. Complementary therapies have also been studied for the reduction of breathlessness in patients with advanced disease. Level one evidence is available for the benefit of both acupuncture and acupressure (Pan et al, 2000).

Conclusions

Given the multi-factorial nature of breathlessness in end-stage disease, no single intervention can be recommended to alleviate breathlessness on its own. *Figure 1* demonstrates the more commonly used interventions. A typical patient may require a combination of these strategies. Thorough assessment of the patient and good communi-

Figure 1. Strategy for breathlessness management at the end of life.



cation are essential. Simple procedures such as positioning and the use of a fan should always be considered. Pharmacological interventions should begin with the use of opioids, titrated as necessary, with the addition of other medications as required.

A proportion of patients become increasingly breathless as they approach the end of the terminal phase of their illness. This can be extremely distressing for both patients and relatives, as well as for the professionals caring for them. In such instances, aggressive management of breathlessness, using both opioids and benzodiazepines, and titrating doses on a very individual basis, may be appropriate. Further research is required to focus on specific targeted therapy, correct method of delivery of pharmacological interventions, which opioid or benzodiazepine can be recommended for best practice and the identification of specific management strategies dependent on aetiology. **BJHM**

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KEY POINTS

- Causes of breathlessness are multifactorial and management requires a combination of interventions.
- Careful assessment and management of reversible precipitating factors is mandatory.
- A multiprofessional approach to teach correct positioning and breathing techniques, anxiety management, communication and maximizing patient control over symptoms are useful non-pharmacological steps.
- Opioid therapy remains the main drug treatment, commencing with a short-acting opioid and titrated accordingly.
- No clear evidence exists to support use of one opioid in preference to another, or to show whether long-acting opioids are as effective as short-acting opioids.
- Oxygen may be useful on an individual patient basis, particularly if hypoxic, but passage of air across the lower trigeminal area of the face may be as effective.
- Benzodiazepines can be effective in combination with other modalities, particularly if anxiety is a component or sedation is required.

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