Pharmacological treatment of refractory breathlessness

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Refractory breathlessness is one of the most common and devastating symptoms of advanced cardiorespiratory disease, both malignant and nonmalignant. In spite of increased interest in research in the last 20 years, there have been few significant advances in the palliation of this distressing condition. The most successful palliative regimens for breathlessness always include pharmacological and nonpharmacological interventions used concurrently. When patients are active, nonpharmacological treatments (e.g., exercise) are the most effective. As the patient becomes more breathless, eventually becoming breathless at rest, pharmacological treatments become more important. Opioids have the most extensive evidence base to guide their use. Other pharmacological interventions may act partly by helping breathlessness (by mechanisms still uncertain) or by treating concomitant precipitating and exacerbating conditions, such as depression and anxiety. A specific treatment to palliate breathlessness remains elusive. The neurophysiological substrate of breathlessness perception is still relatively poorly understood and not well reproduced in animal models. Research using functional MRI and other imaging, with more precise clinical trial methods, may help to bring significant advances. In the next 5 years, novel approaches to delivering opioids may be developed, the effective use of inhaled furosemide may be elucidated and the place of antidepressants and anxiolytics will become clearer. A role for cannabinoids may emerge. New drugs may be developed as our understanding of neurophysiology grows.

Epidemiology & definition

Breathlessness is a common distressing symptom of advanced cardiorespiratory disease, both malignant and nonmalignant in nature. It may be defined as refractory when it persists despite maximal medical and other therapy being given for the underlying condition. It now affects millions of patients throughout the world. Overall, 94% of patients with chronic lung disease, 50% of patients with heart disease [1] and, in the last year of life, 90% of patients with lung cancer [2] and 50–70% of all cancer patients, even those without apparent lung pathology, will experience breathlessness. The prevalence increases as death approaches.

Globally, chronic obstructive pulmonary disease (COPD) has a rapidly increasing incidence and is predicted to be the fourth most common cause of death throughout the world by 2020 [3]. Lung cancer is the most common cancer in men and of increasing incidence in women and, although it is declining in the West as smoking rates decrease, it is becoming more

and more common in other parts of the world. Mesothelioma is increasing in incidence, with the peak estimated to occur in approximately 2020 in the UK. Ischemic heart disease is the most common condition affecting patients in the developed world and, as dietary and working patterns change in the developing world, it is becoming much more common there. Interstitial lung disease is a rare but usually rapidly progressive respiratory disease, with few treatment options, and is associated with severe and frightening breathlessness and cough.

Breathlessness, therefore, will continue to be a significant clinical problem for many years and it is imperative that we find better ways of managing or even preventing its onset. In addition to its clinical and psychosocial effects on patients, the presence of intractable dyspnea is associated with profound social and psychological changes for carers, and, thus, the numbers of people affected by this devastating symptom are even greater than the disease statistics would suggest.

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The definition of breathlessness most commonly quoted was formulated by an expert committee of the American Thoracic Society (ATS), which described it as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interaction among multiple physiologic, psychological, social, and environmental factors and may induce secondary physiological and behavioral responses" [4,5], highlighting the central characteristic of dyspnea that it involves "both the perception of the symptom … and the patient's reaction to it." The 'central processing' of the sensory component of dyspnea by the higher centres in the CNS, thereby reducing or increasing its affective component, offers both pharmacological and nonpharmacological approaches to its management.

In this review, only the pharmacological management of chronic intractable breathlessness, where management of the underlying condition has been optimized by appropriate specialist treatment (medical, surgical or oncological), will be considered. Excellent management of the underlying disease is always the first step and reassessment for the onset of new diagnoses, which may be treatable, should always be undertaken when patients deteriorate over a short period of time. For example, patients with severe breathlessness are less mobile and have a higher incidence of pulmonary embolus than more mobile and fitter individuals. Patients with advanced COPD may develop heart failure or dysrhythmias, such as atrial fibrillation, which may be reversed. Acute breathlessness is not considered and nonpharmacological treatments, although highlighted, are not discussed.

Neurophysiology of breathlessness

The neural control of breathing emanates from an 'automatic' controller located in the bulbopontine brain, which functions to maintain a basic respiratory rhythm and to adjust this rhythm according to metabolic needs. Blood gases and pH are homeostatically maintained in the face of substantial disturbance, through negative-feedback signals from a number of mechanical and chemical receptors throughout the respiratory system, and a common efferent pathway. The bulbopontine controller can be modified or overridden by widespread influences from suprapontine regions of the brain, including the motor cortex and cerebellum. Behavioral control of the breathing apparatus includes intentional control, protective reflexes, such as cough, and emotional influences [6], and, in this respect, the neural control of breathing is atypical of a sensorimotor system.

Not surprisingly, the neurophysiology of breathlessness is intricately entwined with the neural control of breathing. The consensus of opinion is that the brain perceives breathlessness when afferent information reporting the demand for breathing does not match afferent signals reporting the prevailing level of ventilation [7]. The various efferent or afferent signals that might constitute a mismatch are listed in Table 1. Table 1 also attempts to identify the quality of dyspnea thought to be suppressed or generated when the signals are increased. Apart from the neural activation listed, dyspnea can also be influenced by stimulation of receptors in the upper airways, oral mucosa or the

facial nerves, through various stimuli including flow, pressure or temperature [8,9]. It has also been suggested that the shortness of breath during exercise may arise from the projection of limb mechanoafferents or locomotor centre output [10].

The precise mechanism of clinical dyspnea, in its various manifestations, remains obscure. Much of the evidence cited in Table 1 derives from studies of experimental dyspnea in healthy volunteers; however, the concept of mismatch also applies to clinical dyspnea. Thus, in COPD patients, the neural output to respiratory muscles and the mechanical output are higher and lower, respectively, than in healthy subjects. The mismatch here is termed neuroventilatory dissociation (NVD), which the patients register as an increased sense of respiratory effort. The dynamic restriction of volume expansion in COPD patients amplifies the mismatch during exercise, forcing them to hyperinflate; there is a dramatic increase in NVD and dyspnea associated with this [11]. Exertional dyspnea is commonly described by COPD patients as 'inspiratory difficulty' and, as with 'air hunger', probably arises from the projection to the sensory cortex of a copy of the neural output to respiratory muscles and afferent feedback of inadequate volume response from lung and/or chest wall [12]. Other theories are similarly based on the 'mismatch' of neurosensory information; 'length–tension inappropriateness' [13,14] and 'efferent–reafferent mismatch' [15]. It is appealing to speculate that the precise afferent signals involved in the mismatch determine the quality of dyspnea experienced. More detailed reviews of the complex multifactorial causes of breathlessness can be found by O'Donnell *et al.* for COPD [7] and by Booth *et al.* for cancer [16].

A number of functional brain-imaging studies have mapped cerebral activations during dyspnea in healthy volunteers within the last decade [17]. The principal activation was in the insular cortex, cerebellum and the anterior cingulate. More recently, other activations have been reported that may be part of a wider 'affective' response (e.g., the amygdala [18]). Activation of the anterior insular is the most consistently reported response, despite differences in imaging methods and the dyspnea stimulus, suggesting that it is essential for dyspnea perception, although this needs to be verified. The insular cortex is a paralimbic structure, involved in formulating behaviors and learning visceral homeostasis [19]. Electrophysiological and tracer studies in animals indicate that the insular cortex receives neural afferents from respiratory chemoreceptors, pulmonary receptors and medullary respiratory neurones [20]. The challenges ahead include:

- Verification of the seat or the neural network that is essential for dyspnea perception

- Imaging studies of clinical dyspnea – that have not been possible so far

- Separation of activations relating to associated anxiety and affective responses from the sensory input

In summary, the concepts of 'mismatch' and of 'multidimensionality' have provided a unifying framework for the numerous putative neural influences proposed over the last few decades. The neural substrate for dyspnea will no doubt be further refined in

Table 1. Neural activation implicated in the generation or suppression of various qualities of dyspnea.			
Study (year)	Neural signal	Role in dyspnea (when signal increases)	Ref.
Adams *et al.* (1985) Banzett *et al.* (1989 and 1990) Chen *et al.* (1991 and 1992) Shea *et al.* (1993) Banzett *et al.*, (1990) Gandevia *et al.* (1993) Spengler *et al.* (1998) Moosavi *et al.* (2003) Moosavi *et al.* (2004)	Copy ('corollary discharge') of brainstem respiratory motor drive projecting to forebrain	Generation of air hunger	[81] [82,83] [84,85] [10] [83] [86] [87] [88] [89]
Campbell *et al.* (1980) Gandevia (1982) el-Manshawi *et al.* (1986) Demediuk *et al.* (1992) Lansing *et al.* (2000) Moosavi *et al.* (2000)	Copy ('corollary discharge') of cortical respiratory motor drive (voluntary drive) projecting to forebrain	Generation of the sense of work or effort (and suppression of air hunger)	[90] [91] [92] [93] [94] [95]
Killian *et al.* (1980, 1984) el-Manshawi *et al.* (1986)	Mechanoreceptor afferents from respiratory muscles/chest wall	Generation (and suppression*) of sense of respiratory work/effort	[96,97] [92]
Banzett *et al.* (1989 and 1990) Gandevia *et al.* (1993) Shea *et al.* (1993) Spengler *et al.* (1998)	Direct chemoreceptor afferents to forebrain	Generation of air hunger	[82,83] [86] [10] [87]
Demediuk *et al.* (1992) Eldridge and Chen (1992) Manning *et al.* (1992) Banzett *et al.* (1996) Harty *et al.* (1996) Moosavi *et al.* (2004) Vovk and Binks (2007)	Afferent signals from lung irritant or stretch receptors	Suppression of air hunger	[93] [98] [59] [60] [99] [89] [100]
Binks *et al.* (2002) Burki *et al.* (2005, 2006 and 2008)	Afferent signals from J receptors or airway c fibres	Generation of the dyspnea of asthma or chronic heart failure	[101] [102–104]
Li *et al.* (2006) von Leupoldt *et al.* (2008)	Negative psychologic, attention or emotion signals to limbic system	Accentuation of affective valence (unpleasantness)	[105] [18]
Alpher *et al.* (1986) Von Leupoldt *et al.* (2006, 2007a and 2007b)	Positive psychologic, attention or emotion signals to limbic system	Mitigation of affective valence (unpleasantness)	[106] [107–109]

*Both generation and suppression is indicated because afferent feedback from respiratory muscle mechanoreceptors or other chest wall mechanoreceptors may provide information to the brain about both the demand for ventilation and the prevailing ventilation.

the years ahead. Clearly, there are more peripheral and central locations to target for pharmacological dyspnea relief than have currently been ventured. A generic pharmacological intervention that benefits all dyspneic patients will presumably need to target the seat of perception within the limbic system – the challenge here will be one of specificity.

Disease trajectories

In order to understand treatment strategies for breathlessness, it is important to understand the possible different disease trajectories that patients with breathlessness may have.

These disease trajectories were first described by Joanne Lynn and were cited and modified in many palliative care reviews [21]. Cancer is becoming much more of a chronic disease for some

tumors, such as breast cancer; while diseases such as mesothelioma and lung cancer, which are characteristically associated with breathlessness, are still difficult to treat and rapid deterioration is the norm. Patients are, apparently, relatively well until shortly before the disease is diagnosed and then their deterioration takes place over weeks or months: represented in the first curve showing a 'short period of evident decline'. Patients, therefore, have to accept rapidly increasing disability, with frighteningly fast changes in their physical condition. Breathlessness may become continuous, so that patients suffer breathlessness at rest very early on in the course of their diagnosed illness. The prognosis of patients with cancer who are breathless at rest is very limited: in one study in this group, the median survival of such patients was 19 days from the time of participation [22]. Although the
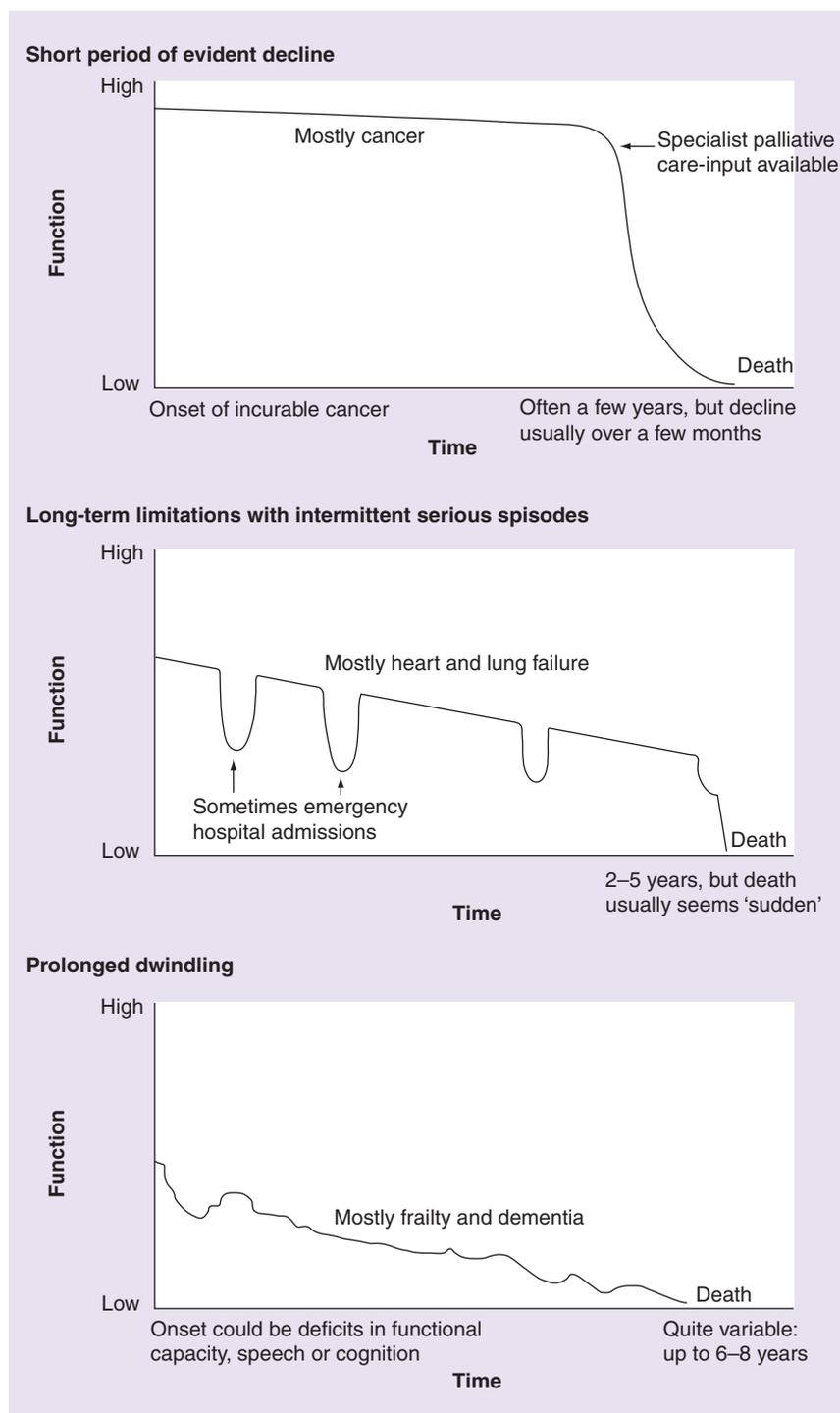
Short period of evident decline

High

Function

Mostly cancer

Specialist palliative care-input available

Death

Low

Onset of incurable cancer

Often a few years, but decline usually over a few months

Time

Long-term limitations with intermittent serious spisodes

High

Function

Mostly heart and lung failure

Sometimes emergency hospital admissions

Low

Death

2–5 years, but death usually seems 'sudden'

Time

Prolonged dwindling

High

Function

Mostly frailty and dementia

Low

Death

Onset could be deficits in functional capacity, speech or cognition

Quite variable: up to 6–8 years

Time

Figure 1. Trajectories in different diseases.
Redrawn wih permission from [52].

decline in patients with cancer is rapid, so that they often look back only 1 year and see huge contrasts between their physical abilities in that short time, they may only have very severe symptoms for a short time and the physicians looking after them will be more willing to use pharmacological treatments, such as benzodiazepines, which they are more reluctant to employ in those with a longer prognosis.

By contrast, patients with COPD develop breathlessness late in the course of their disease, often many years after diagnosis. Although their disease trajectory is one of deterioration, the course is slower and punctuated by episodes of exacerbation, where the patient's condition may be life threatening, followed by an incomplete recovery that takes place over weeks or months. Characteristically, these patients have far more exacerbations in the winter, often precipitated by viral or bacterial upper respiratory tract infections. Patients who have experienced a relatively slow deterioration punctuated by exacerbations may learn coping mechanisms or ways to accommodate the illness; on the other hand, they have to live with devastating breathlessness for many years and spend many years of their life unemployed or unable to carry out their favored occupations or interests. Both they and their families become increasingly socially isolated and impoverished.

Pharmacological treatment
Opioids for breathlessness
Although once feared as a cause of respiratory depression, oral morphine is the mainstay of pharmacological treatment for intractable breathlessness, since its use is supported by the greatest weight of evidence and the greatest history of clinical use. However, there are still important clinical questions that need to be answered regarding the use of opioids for breathlessness, such as the most effective alternative routes, the most effective opioids and the most effective regimens, such as normal versus 'long-acting' or, more correctly, modified-release preparations. The roles of the newer opioids, such as alfentanil, have not been fully elucidated.

The key studies in this area are first the systematic review and meta-analysis of all the primary studies on the use of opioids in dyspnea carried out by Jennings *et al.* [23] and the randomized controlled trial (RCT) of modified-release oral morphine in the palliation of breathlessness published shortly afterwards by Abernethy and Currow [24].

Both of these investigations involved adult patients with intractable breathlessness of any etiology, malignant or nonmalignant. Jennings *et al.* extracted data from double-blind, randomized placebo-controlled trials that used opioids "for the treatment

Table 2. Characteristics of patients in the randomized controlled trial of oral morphine versus placebo in the palliation of breathlessness.

Age (years)	Male (%)	COPD (%)	Cancer (%)	MND (%)	Other (%)	Sup O$_2$ (%)
76 ± 5	73	88	6	2	4	71 (average: 1.4 ± 1.21/min)

COPD: Chronic obstructive pulmonary disease; MND: Motor neurone disease; Sup: Supplementary.
Reproduced with permission from [55].

of dyspnea, secondary to any cause." They conducted 'random-effect meta-analyses' on all the included studies and compared subgroups (e.g., nebulized opioids) by metaregression. Only 18 studies were suitable for meta-analysis and all of these were small, cross-over studies. The largest had only 19 participants in total [25]. Five of the studies included in the review could not be included in the meta-analysis since there was not enough detail "for relevant parameters to be calculated." The meta-analysis showed a statistically significant improvement in breathlessness in patients treated with opioids (p = 0.0008; 95% confidence interval [CI]: -0.50 to -0.13). The available data on nebulized opioids showed that they were no more effective than placebo. Metaregression of subgroups showed a greater effect for oral or parenteral opioids (p = 0.02). The effect on dyspnea was small, approximately 8 mm on a 100-mm visual analog scale (VAS), with a baseline level of dyspnea of 50 mm.

Jennings *et al.* highlighted that, although there were a large number of trials, most of these were single-dose studies, all contained small numbers of participants, many did not measure breathlessness as an end point and there was no methodological cohesion in investigating this topic.

It is interesting that the adverse effects noted in these studies (drowsiness, nausea, dizziness and constipation), which are those expected with opioids, were more common in those patients who were initially opioid naive. There were no reported incidences of respiratory depression or, where blood gases were measured, significant increases in PaCO$_2$.

Jennings *et al.* are updating their systematic review at present and, although the full paper is still awaited (incorporating Abernethy and Currow's RCT), a short systematic review in 2008, by Booth *et al.*, found no new studies that altered the findings of the original paper [16].

The RCT of opioids in the management of breathlessness carried out by Abernethy *et al.* was the first fully-powered RCT on the effect of oral morphine in breathless patients, with the effect on dyspnea, measured by a 100-mm VAS, as the primary outcome measure [24]. Opioid-naive patients from any department of the hospital and in- or out-patients, with breathlessness at rest from any disease, were randomized to receive a standard dose of 20 mg of modified-release morphine for 4 days, followed by 4 days of an identically formulated placebo or *vice versa*. As a crossover trial it was possible to have a relatively small sample size, in spite of the heterogeneity of the participants, since patients acted as their own controls. The minority of patients in this study had cancer (n = 6), as few of these patients were opioid naive; the majority had COPD. Participants had a mean morning baseline dyspnea score of 43 mm (standard deviation [SD]: 26). There was a significant difference between morphine and placebo on the effect of breathlessness, with a relative improvement over baseline dyspnea of 15–22%, with mean improvement in dyspnea intensity of 6.6 mm in the morning (p = 0.011) and 9.5 mm in the evening (p = 0.006) (**Tables 2 & 3**).

The overall improvement in dyspnea was strikingly similar to the change in breathlessness with morphine found by Jennings *et al.*: that is, patients on morphine had a 7–10-mm improvement on a VAS in their breathlessness over baseline values. Although the authors stated that the study was not powered to detect adverse effects, those reported were minimal, and there was no respiratory depression. Patients also generally reported better quality of sleep during the period in which they took morphine.

Anxieties still remain, particularly among respiratory physicians, concerning the use of morphine for breathless patients. The most recent Global Initiative for Chronic Obstructive Lung Disease guidelines that review the use of morphine state that "the use of oral/parenteral opioids are effective for treating dyspnea in COPD patients with advanced disease" [26], but then go on to comment "however some clinical studies suggest that morphine may have serious adverse effects (note that these were unspecified) and its benefits may be limited to a few sensitive subjects…" [201], which seems excessively cautious, both in the light of palliative care experience and the data from the work of Abernethy and Currow and Jennings *et al.* [23,24].

An adequately powered epidemiological investigation to test the safety of opioids across the population of breathless patients is desirable; however, this would require extremely large numbers because the incidence of problems appears low. It may be preferable to target a study to those patients who might be deemed high risk, such as those patients with chronic lung disease who have type II respiratory failure (i.e., with a resting PaCO$_2$ > 6.5 kPa) or who have a history of developing it during exacerbations.

Definitive studies for patients with heart failure are awaited; however, Johnson *et al.* published a feasibility randomized, double-blind, placebo-controlled trial of doses of 5.0 mg of normal

Table 3. Visual analog scale measurements (mm) for patients in the Abernethy and Currow trial of oral morphine versus placebo in the palliation of breathlessness.

Time	Morphine	Placebo	p-value
a.m.	40.10	47.7	0.011
p.m.	40.30	49.9	0.006

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release morphine four-times a day for 4 days, followed by 2 days of washout and then placebo, in patients with NYHA III/IV level heart failure [27]. Six out of ten patients considered that their breathlessness was improved and, on morphine, the median breathlessness score fell by 23 mm (p = 0.022) by the second day of the trial. Again, adverse effects were few. A full-scale RCT is planned.

Prescribing opioids for patients with cancer

At present, based on this evidence and expert consensus [28], it is recommended that opioids are used for intractably breathless cancer patients, particularly those with breathlessness at rest, who have a particularly poor prognosis. The dose can be based on the pre-existing opioid regimen for other conditions, such as pain, when 'as-required' opioids can be given in one sixth of the total daily dose of opioids to be used when breathlessness is poorly controlled. Oral opioids, of course, do not have an immediate effect, as they need to be absorbed through the upper GI tract and there may be significant first-pass metabolism before they reach the blood stream. However, the element of choice offered by 'as-required' opioids for patients, coupled with an opportunity to initiate a treatment at the time of their choosing, may help to explain why some patients find this a useful strategy.

In patients with nonmalignant disease, prescribing is a little more complex.

Prescribing opioids for patients with COPD

These patients have often been breathless for a long time and a small proportion will be hypercarbic. They may associate opioids with cancer (and, unless carefully explained, they may think that they have cancer that is being concealed from them) and, often, with imminent death.

Of course, there is good reason to be judicious in the use of opioids for patients with nonmalignant respiratory disease, but morphine is increasingly recognized in respiratory medicine circles as one of the best therapeutic agents that we have for palliation [26]. In contrast to cancer, many patients with COPD eligible for opioids have been breathless for years, and there is no immediate rush to titrate up to a significant dose over a short period of time. We would advise the use of a 1-mg starting dose of morphine, once a day, increasing to a 1-mg twice daily dose during the next week and increasing by 1 mg a week until the lowest possible effective dose of treatment for breathlessness is found. Some experts have found that doses as small as 0.5 mg twice daily can have a significant, positive impact on an individual's quality of life [29]. Morphine is excreted from the body via the kidneys and the half-life of morphine and its active metabolites will be prolonged in renal impairment, which may be present in frail, elderly breathless patients, but the reported overall effectiveness of morphine at these low doses cannot easily be explained on pharmacodynamic grounds. With low initial doses, adverse effects are less likely, can be anticipated and treated rapidly and neither patients nor their treating clinicians will feel concerned about overdosage on this conservative regimen. Patients may also be given the option of using a limited number of extra 'as-required' doses of oral morphine during the titration period, which will help to guide the final dose.

In cases where there is real resistance or significant anxiety on either the patient's or the clinician's part, the first doses can be administered under the supervision of out-patient assessment clinics and 'before' and 'after' blood gases or, alternatively, patients may be admitted to a specialist palliative care unit for titration of opioids.

Once initiated, the dose of morphine needs to be reassessed. With such cautious starting doses and slow upward titration the reassessment can be weekly: simple quantitative measures of effectiveness could include a numerical rating scale (NRS), with anchors such as 'no breathlessness' and 'breathlessness as bad as can be' or with the use of the Borg scale, both of which can be used during telephone consultations.

Prescribing opioids in patients with other cardiorespiratory diseases

Many patients with other cardiorespiratory diseases and breathlessness are not referred to palliative care services, when this should be a first step for patients with severe breathlessness, rather than simply prescribing them opioids. However, there is evidence that opioids may be helpful in relieving the breathlessness associated with any advanced disease and that they should be one of the therapeutic options.

Patients with interstitial lung diseases often have stimulation of their respiratory centre and may particularly benefit from opioids. They may be hypoxemic but are rarely hypercarbic. It is sensible to start on a low dose, as for COPD, since, again, most of these patients will be treated in the community and may not be monitored closely.

In patients with maximally-treated chronic heart failure and breathlessness, Johnson's feasibility study does show that opioids have promise in this group [27] and a cautious titration, similar to that used for patients with COPD, would be the approach that we would recommend.

Opioids have unwanted side effects, such as nausea, vomiting and sedation, which can alienate patients from their use if they accompany their first experience of opioids. These side effects are generally less severe if anticipated, explained and treated early or even prophylactically (e.g., if a patient has already experienced nausea for other reasons we recommend starting them on an antiemetic [e.g., haloperidol for the first 3 days of starting an opioid])). It is helpful to leave 2 days supply of antiemetic in the house for patients being treated in the community, so that patients can initiate treatment for nausea immediately, which lowers the risk of early alienation. Starting aperients (and advising patients how to titrate them, as there is marked interindividual variation in the dose needed) before constipation becomes a problem is essential. Severe constipation, with accompanying straining at stool, will increase abdominal pressure, exacerbating breathlessness, particularly in COPD patients who are already hyperinflated.

Patients should be alerted to the possibility of the adverse effect of respiratory depression, which is preceded by sedation: oral opioids have a built-in safety factor for this reason,

provided titration is slow. If patients are excessively sleepy they should not take their next due dose and seek medical advice. Written information is always valuable and close contact with any community team involved in the patient's care is essential – they must also be told exactly what the patient and family have been advised. The absence of reported incidences of respiratory depression from both the Jennings' systematic review [23], and the Abernethy and Currow trial is reassuring [24]. There has also been a recent small study from Germany [30], which found that there were no changes in PaO_2 and $PaCO_2$ (measured transcutaneously) after opioid administration and, although this is a small single-dose study, it adds to the small body of evidence in this area.

Other authorities have felt able to use higher initial starting doses of opioids (Currow D, Pers. Comm.) who are carrying out dose-finding studies with modified-release morphine at present, routinely start patients on 10 mg of modified-release morphine (MST®) without concern and have experienced no problems.

Which opioid?
There is currently no evidence as to which strong opioid is the best for the relief of breathlessness. The studies included in a review by Jennings *et al.* examined morphine, diamorphine and dihydrocodeine. In practice, morphine is the most widely used opioid. As episodes of dyspnea ideally demand a rapid onset of action of the opioid, alternative routes of application have been explored. Due to its lipophylic nature, fentanyl seems a good drug for rapid relief. It has been used predominantly in cancer patients by various routes, including via nebulization (with doses of 25 µg in 2 ml saline) [31], transmucosally with doses of 400–1200 µg [32] and as a nasal spray with 4-hourly doses of total daily dose (e.g., 400 µg in patients with 100 µg/h transdermal therapeutic system fentanyl) (Sitte T, Pers. Comm.).

Benzodiazepines
Benzodiazepines are regularly prescribed in patients with breathlessness and cancer or at the end of life, in other diseases. There are theoretical reasons why they may be helpful: they are anxiolytics and many authorities feel that anxiety is a potent exacerbator or precipitator of episodes of breathlessness. There is, however, little good evidence. The short systematic review published in *Nature* revealed that there were no meta-analyses or RCTs for the use of benzodiazepines in cancer dyspnea and the evidence for their use in COPD and other nonmalignant disease is similarly scanty [16]. A Cochrane Review is planned by Simon *et al.* (Simon S, Pers. Comm.).

In patients with nonmalignant disease, the lengthy prognosis combined with the potential of benzodiazepines to create dependency has meant that they are rarely used and that nonpharmacological methods for managing dyspnea are favored. Alternatively, buspirone (see later) may be prescribed. However, oral benzodiazepines, such as lorazepam and diazepam, are frequently used in cancer patients when concerns about dependency fade. However, neither of these drugs are short acting and accumulation and prolonged sedation are possible. The authors prefer to avoid diazepam: if an oral anxiolytic is needed, lorazepam 500 µg–1 mg used up to three-times daily at times of need is recommended, with nonpharmacological strategies used preferentially. Midazolam, only available for parenteral use, has a half-life of 5 h and no active metabolites and, therefore, has advantages when patients are in hospital and need temporary sedation (perhaps at night) or anxiolysis. However, the use of midazolam earlier in the disease course is limited because of the need to administer it parenterally.

The existing evidence is not even as strong as that for phenothiazines and the latter is preferred by some authors at the end of life [33]. This uncertainty about the role of benzodiazepines and phenothiazines is clearly unsatisfactory and studies powered to investigate the effectiveness of these drugs are urgently needed.

Buspirone
Buspirone showed early promise as an agent that could help reduce breathlessness. It is a serotinergic anxiolytic agent, and, thus, it may be possible that it acts through postulated serotinergic pathways in the respiratory centre of the brain stem. It is not a sedative, nor does it have anticholingergic properties and it is a respiratory stimulant in animals. At present, the only evidence is from two small studies in patients with COPD, which investigated the use of buspirone in breathlessness: Argyroeoulou *et al.* (n = 16) [34] and Singh *et al.* (n = 11) [35]. Both studies examined the effects of buspirone on exercise tolerance, anxiety levels and breathlessness in patients with severe COPD. These studies looked at slightly different patient populations. Singh *et al.* used anxiety as an inclusion criteria measured on the Speilberger State/Trait Anxiety Inventory Scale; patients had to have a score of over 50 to participate. Argyroepoulou *et al.* did not measure anxiety for patients at baseline, but it was an outcome measure in addition to other psychological symptoms, such as depression. Argyroepoulou *et al.* found improvements in breathlessness, exercise tolerance and anxiety in their patient group who received buspirone; whereas, Singh *et al.* found no difference between buspirone and placebo in measures of anxiety and breathlessness [35]. Both studies are small and were carried out 15 years ago and need to be repeated in fully-powered trials, since the data is conflicting and the answer would be very helpful in clinical practice.

Currently, there is a randomized, placebo-controlled trial underway, investigating the use of buspirone in patients with breathlessness associated with cancer, who are receiving chemotherapy: 376 patients need to be recruited and the trial, which began in November 2002, is predicted to finish in November 2008 [202].

There is clearly a need for high-quality studies that investigate the use of anxiolytics in breathlessness. At present, the decision to prescribe has to be made on a case-by-case basis, carefully weighing individual characteristics and the social setting for the patient and considering whether nonpharmacological techniques, including psychological interventions and social support, have been used to their maximum extent. Alternatively, anxiolytics may be considered for a 'fixed term' to control severe anxiety and give patients an opportunity to learn anxiety management

or for other interventions, to improve breathlessness or other problems and so reduce anxiety and the need for pharmacological anxiolysis. A recent review of the qualitative literature by Gysels *et al.* found that breathlessness preceded anxiety, perhaps because the symptom is frightening in itself or because of the worries associated with having a difficult, chronic or life-threatening condition [36].

Sensitive communication is essential for patients to feel 'safe', to express their fears and discuss their concerns without feeling that they are being judged as people 'not coping' or 'panicking' when they feel anxious. Learning anxiety management needs to be a routine part of learning to live with a chronic illness and presented as such.

Phenothiazines
In the UK, benzodiazepines are used to supplement opioids more commonly; however, in Canada and the rest of North America, it may be more common to use levomepromazine for pharmacological management of anxiety [37–43]. Levomepromazine – a major tranquilizer with a wide range of effects (e.g., α-adrenoreceptor blockade) – may cause dysphoria and hypotension in this frail group of patients. Apart from some early work, there is very little published evidence on the use of phenothiazines in breathlessness [38].

Management of breathlessness at the end of life
In end-of-life care, the use of subcutaneous midazolam and parenteral opioids is almost routine in patients with cancer dyspnea. There is one RCT of the use of midazolam in dying breathless cancer patients [44]. It was a relatively large study of 101 patients randomly assigned to one of three groups, with all drugs given subcutaneously:

- Morphine 2.5 mg every 4 h with midazolm 5 mg as needed

- Midazolam every 4 h with morphine as needed

- Morphine 2.5 mg and midazolam 5 mg every 4 h with morphine 2.5 mg as needed

Patients in all three arms of the trials received midazolam and the starting dose (5 mg every 4 h) was higher than recommended in other guidance [45]. Additionally, this was a study conducted at the very end of life and it gives no information to help with the care of patients who are days or weeks away from death. Unfortunately, this trial was something of a missed opportunity, since a placebo would have been both ethical and helpful in the dearth of other evidence to either recommend (or not) the use of benzodiazepines.

Our practice would be to use low-dose midazolam with low-dose morphine or diamorphine at the end of life. Initial doses can be as low as 5–10 mg of midazolam in 24 h with 1.25–2.5 mg as needed up to every hour, according to the patients' needs or wishes to either avoid or embrace sedation. At the end of life, a phenothiazine, such as levomepromazine (orally or by once daily subcutaneous injection), or a butyrophenone, such as haloperidol, may be either added to this combination or may be substituted for

a benzodiazepine if the patients have extreme fear, overwhelming anxieties or elements of paranoia. Using a continuous subcutaneous infusion of midazolam and morphine with 'as-needed' additions is the authors' favored option.

Use of antidepressants in the palliation of breathlessness
It is clear that depression is often undetected in patients with advanced disease and breathlessness [46]. There may be an assumption that patients will be unhappy because of the restrictions imposed by their illness or because they have a life-threatening illness and, therefore, depression is seen as normal and not worthy of treatment. As outlined previously in the physiology of breathlessness, there are very good reasons for thinking that the central perception of breathlessness may be altered by mood states and emotional factors. There are some data to suggest that there are serotinergic pathways in the brainstem respiratory centre [47]. We would recommend that, when seeing breathless patients for the first time, they should always be assessed for depression in a systematic way. This is not necessarily carried out by asking rote questions at the first meeting; however, gaining a general impression of the patient's mood is very important to the management of breathlessness and, second, in a disease where somatic symptoms such as weight loss, anorexia and poor sleep are common, the most helpful questions for discerning whether a patient has breathlessness or not, are emotional and psychological ones. Questions centered on anhedonia and the presence of guilty ruminations are often helpful in discerning the presence of depression that may need pharmacological management. The Hospital Anxiety and Depression Scale (HADS) [48], which is a well validated and widely-used screening tool for these psychological symptoms in the medically ill, may be helpful.

There are no randomized data on the efficacy of antidepressants in cancer dyspnea. These agents are considered useful because of the treatment of depression, which has been shown to exacerbate the severity of symptoms in cancer patients. In addition, the mind–body link in breathlessness is long established and the impact of 'central processing' of symptoms on their severity is accepted. The use of antidepressants requires systematic investigation.

If depression is present, best practice should be followed: pharmacological treatment always needs to be supported by the use of nonpharmacological strategies. In mild-to-moderate depression, nonpharmacological psychosocial strategies may be used alone in suitable patients. In severe depression, or in frail, breathless patients or those near to death, pharmacological treatment will be required first. Interventions, such as cognitive behavioral therapy, do demand commitment and a certain level of cognitive energy and so may not be suitable for the very ill: pharmacological treatment requires at least 2 weeks before it starts to work and so if there is a delay in starting it, physical deterioration may overtake the patient before an improvement is seen. If a person dies in a depressed state, the memories of grieving relatives will be colored forever by this

Table 4. Summary of studies investigating dyspnea relief by inhaled furosemide in humans listed in chronological order.

Study (year)	Subjects (n)	Study design	Dose nebulized	Component of dyspnea studied	Dyspnea induction	Rating method	Result	Ref.
Stone et al. (1994)	Terminal cancer (1)	Single case report			None			[49]
Nishino et al. (2000)	Healthy subjects (12)	Placebo-controlled	40 mg (single)	'Urge to breathe'	(i) Breathhold (ii) hypercapnia plus resistive load	200-mm, 10-point VAS	(i) Median ~30-mm ↓ on VAS during loaded breathing (ii) 50% ↑ in breath hold time	[52]
Hinckley (2000)*	Acute asthma (35)	Double-blind, placebo-controlled	40 mg (single)	'Dyspnea' of acute asthma	None	10-point dyspnea scale	(i) No subjective difference (ii) peak flow unaffected (iii) rescue albuterol unchanged	[58]
Shimoyama and Shimoyama (2002)	Terminal cancer (3)	Uncontrolled clinical series	20 mg (four-times daily)	'Breathlessness'	None	100-mm VAS	55–90 mm ↓ on VAS score	[50]
Minowa et al. (2002)	Healthy subjects (10)	Double-blind, randomized, crossover	40 mg (single)	'Respiratory discomfort'	Hypercapnia by steady state and rebreathe	200-mm, 10-point VAS	(i) Mean treatment effect ~10–15-mm VAS (ii) unchanged hypercapnic ventilatory sensitivity	[110]
Kohara et al. (2003)	Terminal cancer (15)	Uncontrolled clinical series	20 mg (single)	'Sense of effort', 'anxiety' and 'respiratory discomfort'	None	Cancer dyspnea scale	Average ↓ ~2 points CDS	[51]
Ong et al. (2004)	COPD (19)	Double-blind, randomized, crossover	40 mg (single)	'Respiratory discomfort'	Exercise (incremental and constant work)	100-mm, 10-point VAS	(i) Mean ~9-mm ↓ on VAS at isotime of constant work (ii) significant bronchodilation	[56]
Stone et al. (2002)*	Terminal cancer (7)	Double-blind, randomized, crossover	20 mg (single)	'Breathing difficulty' and 'breathing distress'	None	100-mm VAS	VAS scores increased after furosemide	[111]
Moosavi et al. (2007)	Healthy subjects (10)	Double-blind, randomized, crossover	40 mg (single)	'Air hunger'	Hypercapnia with constrained ventilation	100-mm VAS	Mean treatment effect ~13-mm VAS	[53]
Jensen et al. (2008)	COPD (20)	Double-blind, randomized, crossover	40 mg (single)	'Breathing difficulty'	Exercise (incremental)	10-point Borg	(i) ~1-point ↓ on Borg (ii) ↑ exercise endurance	[57]
Laveneziana et al. (2008)*	Healthy subjects (9)	Double-blind, randomized, crossover	40 or 80 mg (single)	'Respiratory effort'	Cycle exercise with external resistive load	10-point Borg	No effect	[64]

*Negative studies.
CDS: Cancer dyspnea scale; COPD: Chronic obstructive pulmonary disease; VAS: Visual analog scale.

sadness. Selective serotonin reuptake inhibitors are the usual first-line antidepressants used today but mirtazepine, a centrally active presynaptic α_2-adrenergic receptor antagonist, is often used in palliative care patients. It is said to improve continuity of sleep and may be helpful in those with prominent anxiety and sleep disturbance.

Inhaled furosemide

An anecdotal case report of a terminal cancer patient first indicated that inhaled furosemide might relieve dyspnea [49]. Since then, several small studies, summarized in TABLE 4, have investigated this possibility. Most report a positive result and little or no change in respiratory drive. However, if inhaled furosemide is to be considered a viable treatment option for dyspnea, several issues need to be addressed:

- Studies that reported the greatest relief were uncontrolled, so that a large placebo effect could not be ruled out [50,51]. Studies that were adequately controlled indicated a small placebo effect;

- Where positive results were reported, a high degree of response variability was evident, even among healthy subjects, in whom very specific forms of dyspnea were induced [52,53]. Understanding why a remarkable degree of relief was observed in some subjects, over and above placebo effects, may provide the key to maximizing efficacy and targeting this therapy to those patients who would benefit most. The small treatment effects reflected in the mean data should not obscure the fact that some subjects responded surprisingly well;

- No dose-finding studies have been published.

Dyspnea relief by inhaled furosemide is most likely mediated by local effects within the lungs. Before it was suggested that it may relieve dyspnea, inhaled furosemide was known to have other actions on lung parenchyma that inhibit cough [54] and protect against bronchoconstrictor stimuli [54,55]. These effects could account for the relief of exertional dyspnea reported in the patients with COPD [56,57], although it did not provide any subjective benefit to asthmatics undergoing an acute attack [58].

Since at least one study reports significant diuresis in healthy volunteers [53], relief due to putative systemic mechanisms secondary to absorption from the lungs needs to be disproved. Systemic furosemide has long been known to relieve dyspnea in advanced heart failure, in which case, unloading of J receptors by relief of pulmonary oedema is the most likely mechanism. However, the role of J receptors in the dyspnea of chronic heart failure is yet to be proven and it is unknown how systemic furosemide affects dyspnea in the absence of tissue-fluid retention.

Inhaled furosemide may also change the sensitivity of lung-stretch receptors that inform the brain about the level of tidal expansion of the lungs; this is a more likely explanation for dyspnea relief in subjects without lung disease [52,53]. Changes in pulmonary stretch receptor activity would mimic changes in tidal lung expansion and the latter is known to influence breathlessness

in healthy subjects [59,60]. This explanation is supported by animal studies; inhaled furosemide inhibits the Na^+-K^+-Cl^{2-} cotransporter in the tracheobronchial mucosa [61], furosemide-sensitive Na^+-K^+-Cl^{2-} cotransporters are expressed by vagal sensory neurons in guinea pigs' airways [62] and the recording of lung stretch receptor activity in rats provides direct evidence that the sensitivity of the receptors changes [63]. It is interesting that inhaled furosemide relieved air hunger associated with hypercapnia with constrained ventilation [53], but did not modify the sense of respiratory effort associated with exercise with added external resistive load [64]. This may reflect a specific modulation to the air hunger or 'unsatisfied inspiration' quality of dyspnea, when pulmonary stretch receptor activity is manipulated.

The use of inhaled furosemide, or an analog with similar action, is particularly desirable for relief of intractable dyspnea because:

- It has few side effects and does not directly affect respiratory drive

- It is a safe and relatively cheap agent, which is already commonly used by the intravenous route in clinical practice

- It could lead to the prospect of developing an 'inhaler' for use in dyspneic patients, akin to bronchodilator therapy in asthma

Role of oxygen in the palliation of breathlessness

The role of oxygen in improving the prognosis of patients with COPD and chronic hypoxemia is well established [65], but its role in the palliation of dyspnea is still controversial in both malignant and nonmalignant disease. Guidelines on the use of oxygen in COPD were published by the Royal College of Physicians [66] and, although there has been some further research since that time, little has changed regarding the available guidance. Briefly, patients who desaturate more than 4% on exercise or who are able to increase their exercise tolerance by 10% by using oxygen 'during exercise' should be prescribed domiciliary oxygen. In the UK, it is now good practice for this assessment to be made by a respiratory physician and many respiratory units now have 'oxygen clinics'. Although universal oxygen exercise testing is still not a reality, much more formal assessment of the need for oxygen has been made in an attempt to cut the use of oxygen 'as an expensive placebo' [67]. It was interesting to note in a study by Eaton *et al.* that, when patients with significant oxygen desaturation on exercise were assessed for oxygen use and then administered it at home, 41% of those who found oxygen beneficial discontinued using it after the study, as they did not judge the impact on their quality of life as sufficient to outweigh the practical difficulties and impositions [68]. The disadvantages of using oxygen include an explosion hazard for those who continue to smoke or have relatives who continue to smoke and the cumbersome nature of, and intrusive noise from, the equipment. Many patients still find going out with oxygen equipment 'stigmatizing' and, although small portable light oxygen cylinders have become available on the NHS, the equipment is still an additional physical burden. Whether these burdens are exceeded by the benefits can be determined by exercise testing.

Oxygen in cancer

Oxygen and air both seem to have some effect with regards to alleviating dyspnea of cancer patients. There is remaining uncertainty in spite of three studies in this area, as to whether inhaled oxygen has extra benefits or whether it is simply the effect of facial cooling, as alluded to earlier [16,69–71]. The pattern of breathlessness in cancer patients is different from that in COPD, as outlined earlier. A fan, with proper explanation and demonstration of its use, is always needed first, along with all the other strategies rather inadequately described as 'nonpharmacological', such as anxiety management, education, cognitive reinterpretation of breathlessness and formal relaxation techniques. It is particularly important that the patient is considered as a whole and the breathlessness 'not separated out' from the person experiencing it. Breathlessness is a centrally-mediated symptom, profoundly affected by psychosocial as well as physical factors [16], but a careful holistic assessment may uncover what seems to be a small subgroup of patients who may benefit from oxygen [22]. The individual who may benefit from oxygen cannot be predicted by their initial level of arterial oxygenation or even marked desaturation on exercise [70]. At present, we recommend that a trial (ideally a formal 'n of 1' trial as described by Bruera [69]) is completed for each individual patient where oxygen is being considered. Where it is needed, the most common prescription will be short-burst oxygen therapy before or after activity or spontaneous episodes of breathlessness [72].

Oxygen in heart failure

Patients with heart failure have a number of pathophysiological changes that alter their possible responses to oxygen, including an abnormal chemoreceptor response to hypoxemia. There is very little data available regarding the use of oxygen in palliating breathlessness in heart failure [73,74]. No specific recommendations based on evidence can be given at this time and it is again suggested that all nonpharmacological measures and other drug therapies, coupled with expert management of the underlying heart failure, are used before oxygen is considered as a palliative treatment.

A fully-powered, international, multicenter RCT of the efficacy of oxygen in reducing dyspnea has just finished recruiting (Abernethy A, Pers. Comm.) and results are expected to become available over the next year or so. Early reports of patients who took part in the RCT and who have now entered the post-trial unblended phase indicate that only 35% of patients in this study have found 16 h a day of oxygen 'not burdensome' and that less than 50% of patients have requested or continued oxygen after the end of the trial [75].

Oxygen in end-of-life care

In the dying patient, oxygen can be of very little use and, in the period leading up to this pharmacological treatment, opioids and benzodiazepines should be introduced and oxygen gradually withdrawn. A full explanation of what is happening is important when oxygen is prescribed or continued in a patient with advanced disease, in order for patients and relatives to anticipate the withdrawal of oxygen as they deteriorate.

Heliox

There are theoretical reasons for believing that a helium/oxygen mixture (Heliox) would be valuable for any patient with an obstructive lesion in their respiratory system. Heliox is much less dense than air, which contains nitrogen and, thus, less turbulence is generated when it flows through a narrow tube compared with air [76]. In recent years, Heliox has been used in diseases where there is increased work of breathing, such as COPD or asthma, to increase alveolar ventilation and oxygenation and reduce oxygen expenditure on respiration. There is one randomized controlled feasibility trial of the effect of heliox versus oxygen-enriched air in 12 patients with lung cancer and dyspnea on exertion [77]. Heliox 28 (72% helium and 28% oxygen) reduced dyspnea on exertion and increased both exercise capacity and oxygen saturation, both at rest and during exertion. The data from it would support a fully-powered trial of heliox in the palliation of dyspnea, separate from any effect on oxygenation. At present, it may be indicated within research studies or when other therapies, rigorously applied, have failed. It remains an expensive drug to use.

Expert commentary

Breathlessness remains a complex, distressing symptom and one that many clinicians feel untrained to manage when it becomes refractory. Acute breathlessness, where there may be a remediable cause and a well-recognized series of diagnostic steps to follow is less intimidating, even if more urgent. Breathlessness at the very end of life is relatively straightforward when pharmacological treatments, including sedation, are simple and effective. It is in the seriously ill patient who is likely to live weeks, months or even years with unremitting breathlessness that the therapeutic difficulties lie.

Accurate diagnostic assessment and maximal treatment of the underlying condition is always the first step as well as finding a way to monitor the impact of any treatments. In the Breathlessness Service at Addenbrookes, we use the Borg scale for anxiety and breathlessness at rest and on exertion, combined with open-ended questions about changes in quality of life. Chronic breathlessness needs to be assessed over a period of time and, at present, one of the limitations to good clinical research is the lack of a suitable assessment tool to capture the multidimensional nature of the symptom. It is important that the clinical teams find a systematic way of measuring whether their treatment strategies work and prioritizing the interventions chosen to fit the individual, their family and the clinical priorities.

Currently, pharmacological treatment alone is insufficient to help breathlessness – a multifaceted approach is needed to produce the best outcomes. This combination of therapeutic strategies targets processes known to be involved in the generation of dyspnea. Psychological interventions, which range from formal cognitive behavioral therapy to mindfulness to education, reassurance and family support reduce anxiety and alter the central perception of dyspnea. Exercise acts both centrally to 'desensitize' the individual to the sensation and, on peripheral muscles, to prevent or reverse

deconditioning, with its impact on muscle structure and function. All breathless patients need to have the full range of nonpharmacological treatments to suit their needs [16] and to have a plan of action for episodes of breathlessness at times of crisis.

Opioids have the best evidence base and the greatest flexibility, in terms of preparations, routes of administration, doses and the possibility of changing drugs if one is poorly tolerated. Patients with severe breathlessness may be helped by opioids and, certainly, they are the mainstay of managing the symptom at the end of life. The oral or transdermal route are to be preferred where possible. At present, nebulized opioids should be kept for clinical trials or extreme situations.

One of the greatest difficulties in helping breathlessness is managing anxiety, and all the available drugs for treating this (e.g., benzodiazepines) have significant disadvantages, even dangers, with regards to their long-term use. Learning nonpharmacological anxiety-management strategies is an effort and one that the severely ill patient or one who has been anxious for decades may not be motivated to undertake. In these circumstances, managing anxiety must take precedence over concerns about dependency if a good trial by a fully-trained psychological therapist has been given and a benzodiazepine or low-dose phenothiazine has been considered. Detection and treatment of depression, using a mixture of approaches, is also fundamental to good care.

Oxygen should only be used after full use of other approaches, particularly the fan, and the impact should be assessed carefully over time. Helium/oxygen mixtures are relatively untried and are not easily available and their use in clinical trials only would be an ideal (unless there is a particularly indication such as respiratory obstruction). However, clinicians may be drawn to using them when the situation is desperate, as there are few adverse effects and the main drawback is expense. Furosemide is a safe, inexpensive drug and may be used when other treatments by specialists or on specialist advice have failed; however, there is currently little evidence, although good theoretical reasons for it being helpful. Other drugs, such as transmucosal opioids and benzodiazepines, are likely to find a place in the treatment of refractory breathlessness in the next few years but, again, their use should be confined to specialist teams or those teams supported by one.

One of the absolutes of managing breathlessness is to support the family or, informally, the carers adequately and to take a systematic, multiprofessional approach to the complete management of the symptom.

Five-year view

There are good theoretical reasons for investigating a number of opioids other than morphine in the management of breathlessness: alternative opioids may have advantages in both having reduced incidence of adverse effects and more convenient and rapidly acting routes. Fentanyl (inhaled and intranasal) is of particular interest for these reasons. Transdermal buprenorphine (the lowest dose of which is equivalent to approximately 5–10 mg of morphine in 24 h) merits testing for patients who require very low, stable doses of opioid and is already documented as being well tolerated and acceptable to patients(Stone P, Pers. Comm.).

The subject of nebulized/inhaled opioids needs revisiting because, although present evidence suggests that it has no advantages over the oral route, there has only been one study performed, which, although adequately powered, did not address all the required issues, such as droplet size and dilution. Further work is now required [78].

Nebulized furosemide is of growing interest and a full-scale, multicentre trial may emerge in the next 3 years. Cannabinoids merit further investigation and some of the difficulties of using this controversial drug group have been overcome in pain studies. All these trials will need to be funded by national bodies, since there is no commercial pharmaceutical interest in these drugs for treating breathlessness. Nutritional approaches to managing breathlessness are also likely to be further investigated and there is the hope that, with early intervention, breathlessness may be prevented as well as certainly reduced by a combination of pharmacological and nonpharmacological interventions.

There is a growing body of opinion that demonstrates that the use of antidepressants needs examination [16,79,80]. Functional MRI is soon to be used (as it is in the treatment of pain) to test interventions used in breathlessness and this may lead to definitive guidance.

Key issues

- Successful palliation of breathlessness is possible, but it is not easy and requires systematic detailed assessment with carefully targeted pharmacological and nonpharmacological therapies.
- Opioids have the best evidence base with regards tosevere breathlessness and, where possible, the oral route should always be used first.
- Opioids other than morphine may have advantages over this drug in specific instances (this has been found in pain management): further work is needed.
- The role of anxiolytics and antidepressants is not yet fully investigated and understood: this is an area where adequately powered randomized, controlled trial evidence is urgently needed.
- Inhaled furosemide shows promise but, at present, should only be used in the context of a trial or urgent clinical need.
- Appropriate nonpharmacological treatments should always be used in conjunction with pharmacological therapy. Pharmacological therapy alone is never enough to give optimal palliation of breathlessness.
- Specific treatments for palliating breathlessness targeted at neurophysiological substrates are required.
- Functional MRI may be a very helpful way of testing interventions once the problem of the examination of people with breathlessness and disease has been overcome (with several trials planned).

The development of a specific compound to target receptors, which modulate breathlessness (peripherally or centrally), will arise one day and perhaps that time is now near.

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