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The etiology and management of intractable breathlessness in patients with advanced cancer: a systematic review of pharmacological therapy

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SUMMARY

Intractable breathlessness is a common, devastating symptom of advanced cancer causing distress and isolation for patients and families. In advanced cancer, breathlessness is complex and usually multifactorial and its severity unrelated to measurable pulmonary function or disease status. Therapeutic advances in the clinical management of dyspnea are limited and it remains difficult to treat successfully. There is growing interest in the palliation of breathlessness, and recent work has shown that a systematic, evidence-based approach by a committed multidisciplinary team can improve lives considerably. Where such care is lacking it may be owing to therapeutic nihilism in clinicians untrained in the management of chronic breathlessness and unaware that there are options other than endurance. Optimum management involves pharmacological treatment (principally opioids, occasionally oxygen and anxiolytics) and nonpharmacological interventions (including use of a fan, a tailor-made exercise program, and psychoeducational support for patient and family) with the use of parenteral opioids and sedation at the end of life when appropriate. Effective care centers on the patient's needs and goals. Priorities in breathlessness research include studies on: neuroimaging, the effectiveness of new interventions, the efficacy, safety, and dosing regimens of opioids, the contribution of deconditioning, and the effect of preventing or reversing breathlessness.

KEYWORDS breathlessness, cancer, carer, dyspnea, palliation

REVIEW CRITERIA

The information in this Review was compiled by searching the PubMed, MEDLINE, CINAHL and EMBASE databases from 1966 to 31 December 2006. Dyspnea has been a research interest for the last 12 years for the authors and articles from personal archives, the unpublished literature, work in progress from colleagues, textbooks, and searching of recent journals and reference lists from papers have also been incorporated. Where possible original studies are cited, but to limit the references cited, recent reviews have been included. Specific details of the search are available on request from S Booth.

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Describe the epidemiology and symptoms of breathlessness in advanced cancer.
2 Describe the pathophysiology of breathlessness in advanced cancer.
3 Identify appropriate nonpharmacologic management of breathlessness in advanced cancer.
4 Describe pharmacologic management of breathlessness in advanced cancer.
5 Specify effective inhaled treatment for breathlessness in advanced cancer.

Competing interests

The authors declared no competing interests. Charles P Vega, the CME questions author, declared that he has served as an advisor or consultant to Novartis, Inc.

INTRODUCTION

Intractable breathlessness is one of the most common and devastating symptoms of advanced cancer.[1–5] It causes physical and emotional distress and social isolation not only for the patients but also for their families and carers.[6,7] The prevalence and severity of dyspnea in patients with cancer increases as death approaches,[2,8] when sedation is often required.[9] There has been little evidence that palliative care interventions improved breathlessness.[10–14] Patients have endured breathlessness with very little effective medical or nursing assistance.[15]

Although there are many clinical, neurophysiological, and psychological similarities with pain,[16] there have not been the same therapeutic advances for the treatment of breathlessness.

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This lack of progress could be because there is no animal model for breathlessness and, therefore, no *in vitro* drug testing is possible. Clinical research is limited in patients with cancer because intractable breathlessness develops late in the disease process, advances rapidly,[2,17] and sick patients cannot comply with experimental conditions such as lying in a MRI scanner. Breathlessness is multifactorial, and the 'induced' symptom in volunteers is unlikely to equal the complex experience endured by patients nearing death. Unlike pain, it is difficult to 'induce' breathlessness in patients at a particular time or in a particular setting for research purposes, the selection of appropriate assessment methods is unclear, and therefore testing therapeutic interventions accurately, including their global effectiveness over a period of time,[18] is problematic.[19–23]

This Review discusses the evidence for our present understanding of the symptom and the many unanswered questions regarding the genesis and management of cancer breathlessness: a short systematic review has been performed of pharmacological therapies, including inhaled treatments. No details of diagnostic or treatment regimens for reversible causes or information on breathlessness in nonmalignant disease are included unless they impinge on the management of patients with advanced cancer. Breathlessness has a profound impact on patients and their families; professional carers can also feel a sense of powerlessness. The terms 'dyspnea' and 'breathlessness' are used interchangeably, but there is a continuing debate about the need for a separate medical word for the symptom.

DEFINITIONS

Breathlessness is a complex experience of the mind and the body. The most recent and widely accepted definition proposed by the American Thoracic Society encompasses this breadth, defining breathlessness 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".[24] Dyspnea has no objective physical signs, although it is often associated with tachypnea, and the severity of dyspnea can only be judged by the patient.

EPIDEMIOLOGY

It has long been recognized that dyspnea is a common symptom in patients with advanced cancer, and its prevalence increases as death approaches, with 70% experiencing dyspnea in the last 6 weeks of life.[2] It is common both in patients with cancer affecting the lungs[3] and in those with cancer originating outside the thorax. In Dudgeon's study of patients attending a general oncology outpatient department, 46% complained of breathlessness, and only 4% of patients had lung cancer.[25] One study of 298 patients with lung cancer reported that dyspnea was present in 60% of patients at diagnosis and 90% in those with advanced disease.[2]

THE EXPERIENCE OF BREATHLESSNESS

Dyspnea is the most common symptom in advanced cardiopulmonary disease of all etiologies. The disease trajectories and therefore the everyday experience of patients with advanced cancer and chronic obstructive pulmonary disease (COPD) are very different. In patients with COPD, intractable breathlessness develops late in the course of the disease, gradually increasing in severity over a period of years. There is a long preclinical phase when patients may not have any respiratory symptoms at all, although lung damage exists (Figure 1).[7,26] There is then a protracted period of gradual decline punctuated by severe exacerbations, which may be life-threatening and require inpatient management. Breathlessness tends to be associated predictably with exertion, until the end of life when it may be present at rest (Figure 1).

Typically, breathlessness in cancer starts episodically,[7,15,27] but with rapid disease progression it may be present constantly, even at rest. Breathless patients with cancer have a short prognosis: in one study, the median survival of participants was 19 days.[19] Intractable breathlessness often develops rapidly in patients who may have felt well, which is especially frightening as patients (and their families) will often recall energetic, easy activity and contrast it with their present inability to walk a few yards. While lung cancer deterioration is especially fast, other tumors may run a more chronic course, with breathlessness becoming prominent near death, linked with general decline into cachexia, fatigue, and weakness. In general, the decline in patients with cancer is more predictable and steadily downward. Equally, other symptoms such as pain may be more debilitating than breathlessness in some patients.[28] In a 'descriptive interpretative' study of patients with cancer cared for by a community palliative care service,[15] patients reported that everyday activities such as climbing stairs (95.6% of patients), walking slowly (47.8%),

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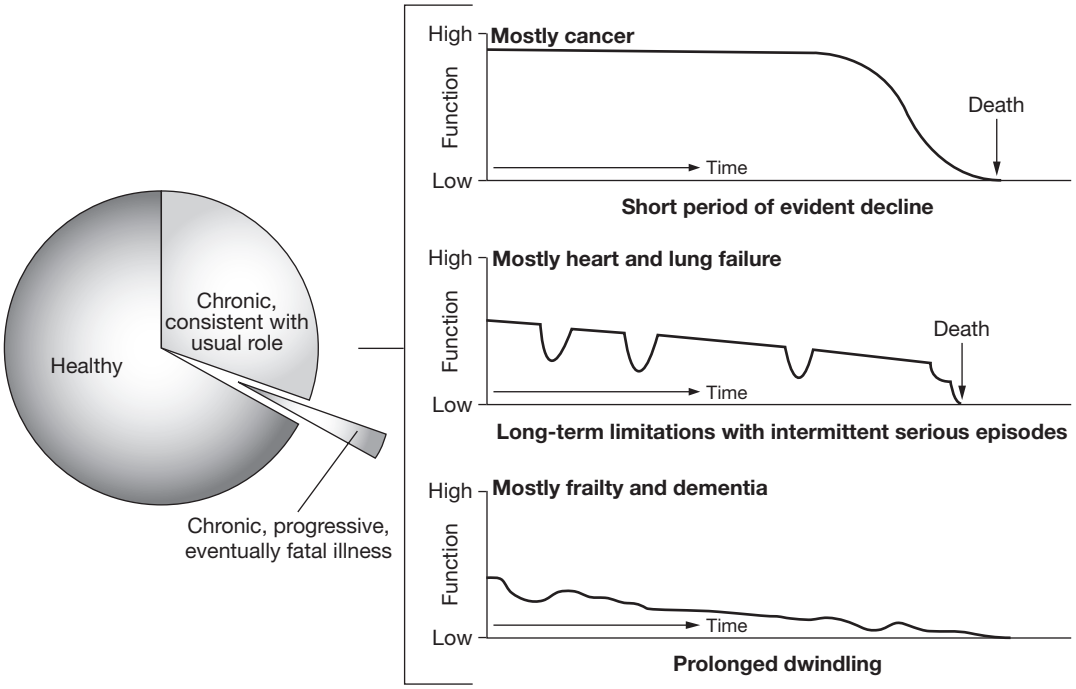

Figure 1 Different disease trajectories for different illnesses. Permission obtained from RAND Corporation © Lynn J (2001) Perspectives on care at the close of life. Serving patients who may die soon and their families: The role of hospice and other services. *JAMA* **285:** 925–932.

or talking or eating (56.5%) could significantly worsen the symptom. Patients perceived that the clinicians caring for them were uncertain how to treat breathlessness and many patients stopped mentioning it. Clinicians need to be trained to diagnose and actively manage breathlessness.

Many studies have confirmed that breathlessness is a particularly distressing symptom for patients and their families.[7,15,29,30] In a qualitative study that investigated the experience of patients with cancer or COPD and carers, a high level of anxiety, particularly at night, was found amongst both relatives and patients.[7] Patients reported thinking "Will I get much shorter of breath? Can I manage it? Is something terrible going to happen?" Carers commented, "…it is terrible to see it…and you feel so helpless, so useless, I don't know how you can help really."

Anxiety and breathlessness

There is uncertainty about the contribution of anxiety in breathlessness—some feel that breathlessness episodes can trigger anxiety,[8] others believe that anxiety precipitates breathlessness.[29] Many strategies that do help to reduce dyspnea in patients with malignant and nonmalignant disease incorporate anxiety management.[7,12,31,32] The incidence of anxiety in patients with the diagnosis of any cancer greatly exceeds that in the normal population.[33] Neuroimaging and psychophysical studies are now helping to assess the contribution of distress and anxiety to the genesis of breathlessness.[34–37]

MRI has demonstrated that the amygdala, part of the limbic system that is associated with fear and emotion, is activated in healthy participants with induced 'air hunger'. Healthy volunteers experiencing induced air hunger describe the feeling as 'terrifying' even though they can halt it at any time. Like pain, breathlessness has sensory (intensity) and affective (emotional) components, which can be managed by different strategies.[38] Two studies by Von Leupoldt and coauthors of normal volunteers in whom dyspnea was induced by artificially increasing the work of breathing, the affective component of dyspnea was reduced by distracting the participants, who read a set text during the period of breathlessness.[34,35] The intensity of the sensation was unaffected. Strategies that are helpful in managing breathlessness in cancer and COPD may not improve symptom intensity, or exercise tolerance, but rather increase the patient's sense of mastery of breathlessness, thereby reducing the associated fear and distress [38,39] Emerging evidence indicates that it is essential to address the psychological needs of carers as individuals, not only as relatives.[40] The experience of living with

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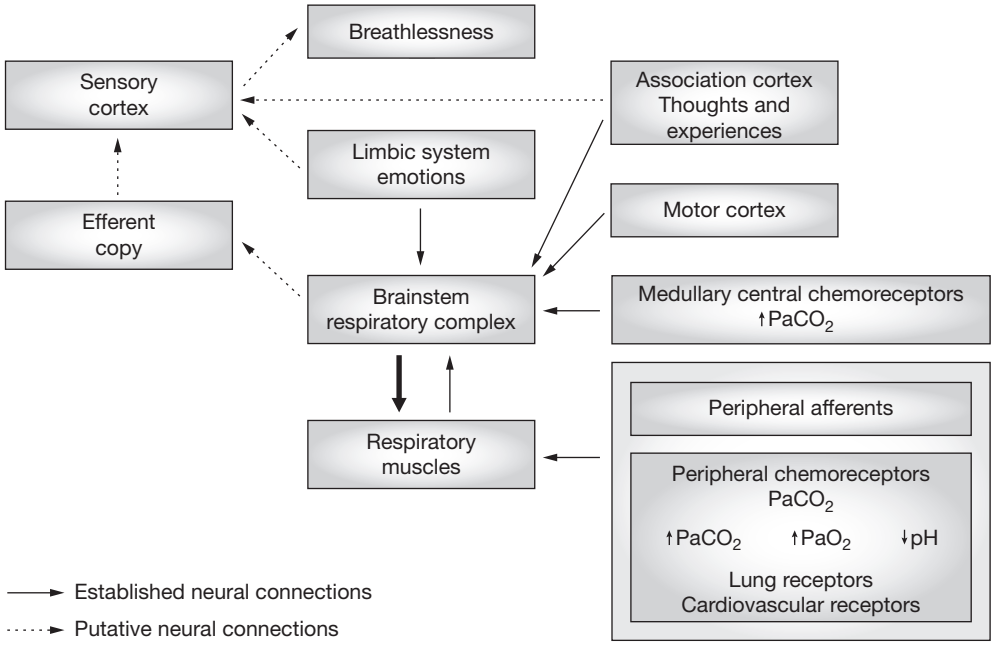

Figure 2 The central genesis of breathlessness. Permission obtained from Elsevier © Stulbarg MS and Adams L (1994) Manifestations of respiratory disease. In *Text Book of Respiratory Medicine*, edn 2, 513–514 (Eds Murray JF and Nadel JA) Pennsylvania: WB Saunders.[42]

someone with intractable breathlessness can cause problems that are separate from the physical burden of caring, particularly anxiety, and relatives may have their own individual fears and emotional burdens associated with the symptom. Many carers are elderly and suffer with comorbidities of their own.

Neurophysiology and pathophysiology

The neurophysiology of dyspnea is complex and poorly understood, but it is clear that there is some similarity with the genesis of intractable pain.[16] Both are somatopsychic experiences arising from multiple receptors integrated at various levels in the central nervous system and therefore susceptible to modulation by both physiological and psychological influences.[41] Dyspnea involves both the perception of the sensation by the patient and his or her reaction to the sensation, which is illustrated schematically in Figure 2. [42]

Normal respiration is a sensorimotor activity involving a respiratory controller in the brainstem, which functions primarily to meet metabolic needs, maintaining blood–gas and acid–base homeostasis through negative feedback mechanisms. The respiratory controller integrates a variety of afferent activity including that of mechanoreceptors in respiratory muscles, of which the diaphragm is the most important; various sensory receptors in the lungs and airways; and chemoreceptors in the carotid bodies and on the ventral surface of the medulla. All these signals are processed in the bulbopontine region of the brain to produce an output that adjusts the rate and depth of respiration appropriately in health.

A more widespread network of suprapontine areas of the brain, including the motor cortex and cerebellum, provide additional 'behavioral' control that primarily functions to implement voluntary control, protective reflexes such as cough, and emotional influences on the respiratory apparatus.[43] These suprapontine influences act via modulation of the respiratory controller in the brainstem or bypass this to influence respiratory motorneurons directly. An afferent copy of the efferent motor command from the respiratory controllers is projected to higher centers registering a conscious awareness of the demand for respiration. In pathological states there is a mismatch between what the body requires and what the respiratory system can provide (Table 1).[24,28,32,44] The center perceives that respiration is insufficient to meet requirements and this mismatch drives the sensation of breathlessness. An up-to-date review of this area has been published by O'Donnell and coauthors.[45] Although the connections shown in Figure 2 have been refined since it was published,[45] we continue to use it with patients because it demonstrates

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Table 1 The causes of breathlessness in advanced cancer.

Causes in patients with cancer	Specific management
Infection/pneumonia	Antibiotics and other standard therapies when appropriate
Comorbid conditions associated with increased dead space, e.g. pulmonary vascular disease, COPD	Optimize medical management of pre-existing/coincident conditions
Deconditioning (lack of exercise)	Rehabilitation (see text)
Anemia	Erythropoietin, blood transfusion where appropriate
Cachexia possibly leading to breathlessness by an unknown mechanism	Prevention of cachexia: activity plus possibly some dietary supplements
Comorbidities associated with respiratory muscle weakness, e.g. myasthenia gravis	Optimum treatment of all comorbid conditions
Respiratory muscle syndromes associated with cancer, e.g. Lambert–Eaton syndrome	Treatment of underlying disease is most effective treatment
COPD associated with lung (and therefore thoracic) hyperinflation, leading to inefficiency of respiratory muscles	Optimum treatment and palliation of COPD
Lymphangitis carcinomatosis	Treatment of cancer, often palliative care, although trial of high-dose steroids (60 mg prednisolone then taper) often used
Tumor obstructing an airway, pleural effusions, pleural disease, e.g. mesothelioma	Standard oncological/surgical treatment according to patient's condition, e.g. radiotherapy and/or stenting, etc.
Fibrosis following pulmonary emboli, radiotherapy, chemotherapy (e.g. bleomycin)	Prevention of fibrosis where possible by early standard intervention in these conditions (e.g. anticoagulation or steroids) or prevention by surveillance during cancer therapy and careful control of chemoradiation dosage
Conditions affecting the compliance of the chest wall/diaphragm, such as hepatomegaly/ascites splinting diaphragm, pleural disease, e.g. mesothelioma, or chest wall infiltration by tumor	Treat as appropriate
Comorbid conditions, e.g. asthma, COPD, interstitial lung disease	Ensure optimum treatment of comorbid conditions
Pulmonary congestion, e.g. from SVCO, heart failure, pulmonary emboli, pericardial effusion	Standard therapy for underlying cancer or treatment of complication of cancer, prevention where possible (e.g. LMWH in high-risk patients)
Hypoxia is a consequence of many conditions associated with cancer including pulmonary emboli, pleural effusions, lymphangitis carcinomatosis, diaphragmatic splinting (e.g. in ascites or hepatomegaly), infections	Assess contribution of hypoxia to breathlessness in that individual and treat conditions as appropriate
Anxieties associated with dyspneic episode reminding the patient they have cancer and are very ill: ▪ Anxiety of dying gasping for breath ▪ Fear/anxiety provoked by idea that breathlessness is in itself harmful ▪ Fear/anxiety because breathlessness at some point may be uncontrollable ▪ Fear/anxiety provoked by the feeling of being breathless ▪ Memory of relative dying with unrelieved breathlessness	Anxiety management using the following alone or in combination: ▪ Nonpharmacological anxiety management strategies (see text) ▪ Pharmacological management of fear and anxiety by phenothiazines, butyrophenones, or benzodiazepines ▪ Cognitive approaches such as cognitive behavioral therapy or education ▪ Availability of clinicians skilled in the management of the symptom

Abbreviations: COPD, chronic obstructive pulmonary disease; LMWH, low-molecular-weight heparin; SVCO, superior vena cava obstruction.

how they can influence dyspnea by addressing its cognitive/emotional aspects. This approach forms the basis of many nonpharmacological approaches to breathlessness control.

Etiology of dyspnea in advanced cancer

The possible causes of cancer dyspnea are illustrated in Table 1. Many studies show that dyspnea in advanced cancer is usually multifactorial, and a

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significant proportion of the underlying causes are irreversible.[8] Palliative care treatments for breathlessness are only partially successful at alleviating this symptom. It is important to reverse what is reversible depending on the patient's physical and psychological condition and personal preferences. Relatively small improvement in a number of different parameters (for example, treatment of pleural effusion or anemia, coupled with reduction in the patient's anxiety and support for the carer) may give significant relief.

The burden/benefit of the intervention for the patient needs to be evaluated by them. If extra visits to hospital are required, will the relief provided exceed the exhaustion incurred? Psychoeducational interventions for patients are less likely to be appropriate than pharmacological ones at the end of life, because of mental and physical fatigue.

Descriptors of breathlessness

Breathlessness, like pain, is a synthesis of a number of different sensations.[46] Simon and colleagues investigated the descriptors that patients use to describe these distinct sensations in the breathlessness of nonmalignant disease, such as 'tightness' in asthma and 'suffocating' in heart failure.[47] It was hoped that, as with pain, the different qualities of breathlessness might indicate specific pathophysiology and therefore help clinical management—for example, indicating specific treatments and reducing the need for invasive investigations, so that patients who were very ill could remain at home and/or would be spared difficult procedures. Wilcock *et al.*[48] started this work in a group of 131 patients with cancer but there was no discernible, consistent link between etiology and cause. The multifactorial nature of cancer dyspnea made it more difficult to investigate this etiology, but more work is planned in this area.

CLINICAL MANAGEMENT

Nonpharmacological interventions

The term 'nonpharmacological' covers an eclectic range of interventions that have not yet been individually or systematically evaluated.[32] Any technique that the patient can initiate at a time of their choosing and manage themselves promotes self-efficacy,[49] which is associated with a reduced risk of depression and increased quality of life in patients with chronic illness. This is important in a symptom that has a rapid onset, probably exacerbated by the anxiety it initiates, and when most of the week is designated 'out of hours' so that only emergency services are available. One of the most helpful strategies that a clinician can offer is to listen to the experience of the patient (and their carers) during a dyspneic episode and write a 'breathlessness plan' with them, incorporating pharmacological and nonpharmacological strategies. This approach can have an immediate impact on patient anxiety as patients and carers start to exert some control over a difficult situation.[40] Many emergency admissions are instigated because of the anxiety associated with breathlessness and yet intractable breathlessness at the end of life may not be most effectively treated in hospital. A prerecorded plan, disseminated and agreed with all concerned, may reduce crisis admissions. There is evidence to encourage the use of the following treatments: the fan, anxiety-reduction training, physical rehabilitation, and noninvasive ventilation.

Figure 3 Specialist physiotherapist demonstrating use of the fan to a volunteer.

The fan

It has been shown that facial cooling in the areas subserved by the second and third branches of the trigeminal nerve will reduce the sensation of breathlessness,[50] and its possible efficacy in patients has been reported.[41] There are no adverse effects, and a fan is a cheap, small, unremarkable piece of equipment which does not draw attention to the user. It is simple to use, allowing most patients to instigate treatment themselves (Figure 3). It is ideal for use in a 'breathlessness/crisis plan'.

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Anxiety-reduction training

Fear and/or anxiety are associated with cancer and breathlessness, and patients and carers need help to find ways to control these distressing emotions. Clinicians need to be careful not to tell the patient or carer that they are 'scared/panicking/anxious' about dyspnea. Instead clinicians should use the words in questions or statements such as, "Some people have told me that they felt a bit panicky during a breathlessness attack—do you ever feel like that?"[7] It is counterproductive to tell a breathless patient to 'calm down' and more helpful to approach anxiety reduction simply by routinely teaching it as part of a 'breathlessness management program'. The method needs to fit with the patient's and relatives' philosophy of care. The method can include the following: learning diaphragmatic breathing and reducing hyperventilation; relaxation techniques such as progressive muscular relaxation; self-hypnosis;[51] visualization and guided imagery;[51] and distraction.[35] Using cognitive techniques (e.g. from formal competency-based training to education) is also an option: simply understanding that breathlessness is not of itself harmful may reduce anxiety. There are many other methods;[49] the key is to suit the technique to the patient.

Physical rehabilitation

It is now well established that pulmonary rehabilitation can reduce dyspnea and improve quality of life in patients with COPD,[39,52] even those who are severely disabled. These programs include exercise training, which can be associated with substantial reductions in blood lactate levels, minute ventilation, and heart rate monitoring at a given level of exercise. In addition, significant improvements can be seen in metabolic enzymatic capacity in the leg.[53,54] In two studies it was noted that breathless patients were often prevented from exercising as much by leg fatigue as by dyspnea.[55,56] There is no comparable research evidence in patients with cancer, but the work in COPD suggests that physical deconditioning, a result of not exercising, exacerbates dyspnea. In patients with cancer, it is important to encourage physical and mental activity, counteracting the effect of well-meaning exhortations to rest. An individual exercise program, modified as the disease progresses, may help; however, the effects on reducing dyspnea of the early institution of exercise need evaluation.[57]

Noninvasive ventilation

There are case histories and reviews of using noninvasive ventilation in patients with advanced cancer[58] to prolong the life of a dying patient who wants to achieve a specific goal, not primarily to reduce dyspnea. The literature relating to patients with COPD suggests that noninvasive ventilation might have a role in symptom control. Formal trials are now needed to investigate its role in palliating dyspnea in advanced cancer.[59]

Pharmacological management

Opioids

There are good data to show that opioids are effective in treating breathlessness: most evidence to date comes from nonmalignant disease.[60,61] Jennings *et al*. completed a systematic review of all the use of opioids in breathlessness, using a standard methodology.[61] They included double-blind, randomized, placebo-controlled trials of opioids for dyspnea from any disease, conducted a meta-analysis on all included studies with adequate data, and compared subgroups (e.g. nebulized opioids) by meta-regression. They reviewed 18 studies and the meta-analysis showed a statistically significant positive effect of opioids on the sensation of breathlessness ($P=0.0008$). Meta-regression of subgroups showed a greater effect for oral or parenteral opioids than for opioids given by the nebulized route, which were no better than placebo. This finding confirmed standard teaching based on a study by Davis *et al*.[62] of oral versus nebulized opioids, which were used because opioid receptors were known to be distributed throughout the respiratory system. Case reports and series have reported benefits in individuals.[63,64] Davis and coauthors found that 50 mg of nebulized morphine were almost as effective as 5 mg of oral morphine. They postulated that any effect was from systemic absorption, with only 10% of the dose reaching the circulation.[65] This review has not found any evidence that strengthens the case for nebulized opioids, but an adequately powered study using different particle sizes would help address the question definitively.

Abernethy *et al*. [60] carried out an adequately powered randomized controlled trial of oral morphine in patients with breathlessness at rest. In this study, only 6 of 38 patients completing the study had cancer, because of difficulties recruiting cancer patients who were opioid-naive. Patients 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. There was a 5–10% (7–10 mm on a 100 mm visual analog scale) improvement in dyspnea over baseline in all patients, who also reported better sleep during the period in

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which they took morphine. The authors stated that the study was not powered to detect adverse effects but these were minimal, and there was no respiratory depression.[60]

Although there are many publications reporting the use of opioids in dyspneic patients, most are case reports or series or preliminary studies. So whilst it is clear that opioids can help cancer dyspnea, questions still remain regarding the optimum starting dose, regimen, opioid choice, choice of modified or normal-release formulation, and the indications for parenteral use. An adequately powered epidemiological investigation to test the safety of opioids across the population of breathless patients is needed as there is still reluctance among some clinicians to use them. Excess mortality with the use of opioids has never been demonstrated in any studies completed thus far.

Phenothiazines

There are no randomized controlled trials of phenothiazines in patients with cancer. The use of these agents is predicated on evidence in COPD and normal volunteers.[66–71] These agents are often preferred to benzodiazepines when sedation or anxiolysis is needed in severe breathlessness.[69–72] The evidence suggests that it may be most effective to institute anxiety-reduction training for patients early in the course of managing cancer and breathlessness as the disease progresses. A low dose (6.25 mg) of oral levomepromazine could be added for patients still suffering intrusive anxiety. Phenothiazines can be administered orally, but they have long half lives and a wide spectrum of possible adverse effects, although these have not been reported extensively in the cancer literature.

Benzodiazepines

There are no meta-analyses or randomized controlled trials of the use of benzodiazepines in cancer dyspnea but they are widely used, often empirically, for anxiety.[73] The existing evidence is not as strong as that for phenothiazines, and the latter may be preferable when patient fear is prominent at the end of life.[74] This uncertainty is clearly unsatisfactory, and studies powered to investigate the effectiveness of benzodiazepines are urgently needed. The addition of midazolam to morphine for control of cancer dyspnea at the end of life has been examined;[75] however, the starting dose for many patients (5 mg every 4 h) was higher than recommended in other guidance.[76]

In addition, all patients received midazolam and no placebo control group was included. A placebo group would have been both ethical and helpful in the absence of randomized controlled trial evidence to recommend the use of benzodiazepines.

Present evidence suggests using midazolam at low doses in addition to morphine at the end of life: for example, 5–10 mg in 24 h subcutaneously with 2.5–5.0 mg as needed, titrated according to the patient's wishes. The addition or substitution of levomepromazine or haloperidol is recommended by the authors if fear, rather than anxiety, becomes overwhelming or for sedation at the end of life.

Oral benzodiazepines such as lorazepam and diazepam are frequently used in patients with cancer when concerns about dependency fade. Nonpharmacological strategies are preferable; however, neither of these drugs is short acting, and accumulation and prolonged sedation are possible. Midazolam, only available for parenteral use, has a half life of 5 h and no active metabolites and is, therefore, better when patients want temporary sedation.

Oxygen

Evidence from randomized controlled trials suggests that both oxygen and air can reduce dyspnea in patients with cancer.[77,78] It seems that it is not the correction of hypoxemia that is important, but rather the flow of gas. Hypoxic patients may not be dyspneic and, if they are, correcting the hypoxia does not necessarily lessen it. The mechanism of action of oxygen is uncertain; it might be related to activation of the trigeminal nerve or cooling of receptors in the upper respiratory tract.

At present, even patients who are intractably hypoxic with cancer should be offered and taught how to use a fan before being offered oxygen or air to inhale. Oxygen should only be used after a formal trial[78] of its effectiveness for dyspnea in that individual as there are no predictive factors to help identify which patients would benefit most. There is undoubtedly a subgroup of patients who obtain substantial benefit from oxygen or air inhalation.[23,79] Short-burst oxygen can then be offered if the patient remains dissatisfied with the fan used in combination with other evidence-based pharmacological and nonpharmacological treatments.[80] A fully powered international multicenter randomized controlled study of the efficacy of oxygen in reducing dyspnea is underway (D Currow, personal communication).

Heliox

Helium is less dense than air and when mixed with oxygen replacing nitrogen in air (heliox) it reduces

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turbulent flow in narrowed airways, reducing the work of breathing and improving alveolar ventilation.[81] It has long been used in patients with airway obstruction as a bridging maneuver until definitive treatment, but is not usually in long-term use, partly because of its cost. There is one randomized controlled trial of the effect of heliox versus oxygen-enriched air in 12 patients with lung cancer and dyspnea on exertion.[82] 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. This was a preliminary study, but the role of heliox clearly warrants a full trial in cancer dyspnea. At present it is best used when other therapies, rigorously applied, have failed, or within a research context.

Inhaled furosemide

A number of case reports and uncontrolled trials of inhaled furosemide have indicated that it might relieve dyspnea in terminal cancer patients.[83–85] Furosemide is a commonly prescribed loop diuretic. When inhaled as a mist it has a variety of actions on lung parenchyma that inhibit cough and protect against bronchoconstrictor stimuli.[86] These actions are not an adequate explanation of breathlessness relief in the absence of asthma or other lung diseases. Studies of experimental breathlessness in healthy subjects indicate that breathlessness relief might be mediated by modulation of sensory afferent signals from irritant or stretch receptors.[87,88] Adequately powered randomized controlled trials in patients with cancer are needed to address unexplained variability and evidence of placebo effects. If proven effective, inhaled furosemide would be a simple and cost-effective treatment that does not suppress breathing, elicit sedation, or have extensive side effects.

Antidepressants

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 patients with cancer. 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.

CONCLUSIONS

Breathlessness remains a devastating symptom, which we are unable to control successfully at present. A careful assessment of the patient with the best diagnosis of the possible cause(s) of breathlessness, reversal or improvement of the symptoms, and pharmacological palliation is a first step. This approach needs to be allied to a strategy to increase the patient's mastery of the symptom and reduce the distress, improving the quality of life for carers and having a significant impact on the patient's and family's sense of wellbeing. The latter is accomplished by taking a systematic and multifaceted approach to this complex symptom using the best evidence presently available. To ensure future therapeutic progress with breathlessness, effective collaboration is needed between the research and clinical disciplines of primary and palliative care, oncology, respiratory and cardiac medicine, the social sciences, psychology, physiology, and imaging to find new, effective treatments.

In the meantime, clinicians need to ensure that they manage breathlessness actively and hopefully, with the patient's ambitions and physical status guiding therapy. The strategy will need constant review because the condition of the breathless cancer patient changes rapidly. Caring for the breathless patient involves the help of colleagues in other specialties and professions to be certain that the patient and the patient's family are getting the best treatment presently available for this complex and difficult symptom that affects every facet of life.

Supplementary information in the form of a table is available on the *Nature Clinical Practice Oncology* website.

KEY POINTS

- Breathlessness is a common, poorly controlled symptom that is distressing for patients and their families, and should be actively managed
- Make the best diagnosis possible of the cause(s) of breathlessness, treating appropriately depending on the patient's physical status and expressed wishes
- All comorbidities should be optimally treated, with specialist advice sought when necessary
- It is important to help patients learn a range of nonpharmacological techniques to control breathlessness and the anxiety and fear associated with it; every patient needs to know how to use a fan
- Whenever possible, the oral route is preferable when using opioids for intractable breathlessness
- Use sedation at the end of life for uncontrollable, distressing breathlessness and let patients know that this will be available if needed

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Competing interests

The authors declared no competing interests.

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