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# Breathlessness in cancer patients

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ABSTRACT

Breathlessness (or dyspnoea) is a common symptom experienced by cancer patients. It may be iatrogenic and is often caused or aggravated by co-morbidity. Recent studies have elucidated the neural and chemical controls of breathing which may be involved in the production of dyspnoea. A rational approach involves making a diagnosis of aetiology and treating reversible causes wherever possible. The main approaches for palliation of dyspnoea include anti-cancer treatments; drugs; oxygen and airflow; non-medical approaches. Further research is needed to clarify the best pharmacological regimens and the place of more invasive interventions.



## 1. Definition

Breathlessness is defined as the subjective experience of discomfort in breathing that consists of qualitatively distinct sensations that vary in intensity. It arises from interactions among physiological, psychological, social and environmental factors; and it may induce secondary physiological and behavioural changes.

Because patients may use different words to describe their difficulty in breathing, for the international perspective in this article we will use the Greek-derived term 'dyspnoea' to cover all such experiences.

## 2. Epidemiology

Dyspnoea is experienced by many patients at all stages of a cancer illness; it is important to be aware that it may be caused by co-morbidity as well as the cancer. Relevant common co-morbid conditions include chronic obstructive pulmonary disease (COPD), heart failure and progressive neuromuscular disease as in motor neurone disease. In the cancer population, dyspnoea is not only associated with primary lung cancer; a Canadian study found that out of 923 cancer out-patients, 46% reported breathlessness but only 4% had lung cancer and 5.4% had lung metastases.[1] Cancers in which at least 50% of patients reported breathlessness included lung, lymphoma, head and neck, genito-urinary and breast. Prevalence of dyspnoea is compared to the other respiratory symptoms of cough and haemoptysis in Table 1.

In many cancers and other chronic conditions, dyspnoea becomes increasingly prevalent and refractory to treatment as the disease progresses. In series of terminally ill cancer patients, the presence of dyspnoea is a particularly adverse prognostic factor. On the other hand, in early stage incurable disease, dyspnoea has not been found to be associated consistently with a poorer survival, even in lung cancer.[2]

## 3. Iatrogenic causes

Dyspnoea may arise during the course of anti-cancer treatment as an adverse effect or toxicity. Pain on inspiration after thoracic or abdominal surgery is usually short-lived, but should be treated actively as hypoventilation can lead to post-operative chest infections. Oncologists will be aware

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**Table 1 – Prevalence of respiratory symptoms in cancer patients**

| Source | Primary site | Stage of disease | *n* | Cough (%) | Haemoptysis (%) | Dyspnoea (%) |
|---|---|---|---|---|---|---|
| Hopwood and Stephens[1] | SCLC | Advanced | 232 | 81 | 26 | 87 |
| Hopwood and Stephens[1] | NSCLC | Advanced | 423 | 87 | 36 | 86 |
| Bergman et al.[4] | NSCLC | Inoperable | 833 | 39 | 5 | 47 |
| Hoilen et al.[5] | NSCLC | Advanced | 673 | 86 | 41 | 87 |
| Portenoy et al.[2] | Breast | Mixed | 70 | 37 | nr | 26 |
| Portenoy et al.[2] | Colon | Mixed | 60 | 22 | nr | 29 |
| Portenoy et al.[2] | Prostate | Mixed | 63 | 26 | nr | 25 |
| Portenoy et al.[2] | Ovary | Mixed | 50 | 29 | nr | 25 |
| Ng et al.[3] | Mixed | Terminal-hospice | 100 (59 with cancer) | 52 | nr | 61 |
| Morita et al.[13] | Mixed | Terminal-hospice | 350 | 29/48[a] | nr | 33-66[a] |
| Anderson et al. | Mised | Palliative care | 213 | 26 | nr | 49 |

Table adapted from Ahmedzai SH. Cough in cancer patients. *Pulm Pharmacol Therap*. 2004; 17: 415-423 (Ref. 3).
a First figure is at admission: second figure is near death.

that radiation therapy involving the thorax may cause acute self-limiting lymphocytic alveolitis or hypersensitivity pneumonitis; after several months or years some patients progress to pulmonary fibrosis with dyspnoea and cough.[3] Bronchiolitis obliterans organising pneumonia (BOOP) can occur with both radiation therapy and drug treatment, including herceptin. Chemotherapy agents such as busulphan may cause acute or subacute idiopathic pneumonia syndrome (IPS) or delayed pulmonary toxicity syndrome (DTPS). Anthracyclines and herceptin are associated with a risk of cardiotoxicity, which can lead to heart failure. Dyspnoea, cough and reduced exercise tolerance are features of all these syndromes.

## 4. Pathogenesis

In recent years, the complex mechanisms underlying the experience of breathlessness have been elucidated using techniques of pulmonary physiology, exercise testing, neuro-imaging and qualitative research.[4,5] Dyspnoea in cancer is the end result of many pathways of pathophysiological changes that occur in patients who have thoracic involvement; co-morbidities (eg COPD or heart disease); muscle wasting due to cachexia; deconditioning associated with restricted mobility; and the effects of ageing (Table 2).

The main causes of dyspnoea are

- increased chemical or neurological drive to breathe, eg by stimulation of chemoreceptors
- increased work of breathing, eg in cardiac failure, pleural effusion
- decreased neuromuscular power, eg in cachexia

In advanced stages of disease, especially if there is cachexia, there is a combination of these factors.

### 4.1. *Chemical and neurological drives*

The chemical drives which control normal respiration and which may be heightened in disease are hypercapnia and hypoxia.

- **hypercapnia** is detected primarily in the medullary chemoreceptors (and partially in carotid bodies)
- **hypoxia** is detected in the carotid bodies

#### 4.1.1. *Chemoreceptors*

The central medullary chemoreceptors respond rapidly to CSF $pCO_2$ (actually pH) which reflects closely arterial $pCO_2$. Peripheral carotid body receptors respond primarily to decreased $pO_2$ and are also sensitive to decreased arterial pH, respiratory oscillations of $pCO_2$, increased blood temperature and chemical stimulants.

**Table 2 – Causes of dyspnoea in cancer patients**

| Organ system | Pathogenesis | Cancer | Co-morbidity |
|---|---|---|---|
| Pulmonary | Airflow obstruction | Bronchial obstruction, stridor | COPD; asthma |
| | Reduced lung compliance | Pneumonitis; pulmonary fibrosis; lymphangitis | Emphysema; effects of ageing |
| | Pleural effusion | Pleural spread | Heart failure |
| | Chest wall restriction | Mesothelioma | Neuromuscular disease |
| | Diaphragm restriction/ inefficiency | Ascites; cachexia | COPD |
| | Ventilation-perfusion mis-matching | BOOP | Pulmonary embolism |
| Circulatory | Pump failure | Pericardial effusion | Chronic/acute heart failure |
| | Hypovolaemia | Too rapid drainage of ascites | Bleeding |
| Systemic | Anaemia | Chemotherapy; marrow infiltration | Chronic disease |

In normal people, the drive to hypercapnia is more sensitive than the drive to hypoxia. However, hypercapnic drive may be blunted in patients with long-standing lung disease, such as patients with advanced COPD who may then become unduly sensitive to changes in oxygen tension.

#### 4.1.2. *Peripheral neurological drives*

The peripheral receptors which are important for the regulation of breathing and the pathogenesis of dyspnoea include mechanical stretch receptors in the chest wall and diaphragm muscles; stretch receptors in the airways; and j-receptors in the lung parenchyma. These send afferent signals to the brain about the ability of the respiratory pump and the lungs to provide the necessary ventilation for the current level of activity.[4,6] In COPD, there is hyperinflation and reduced compliance of the lungs and these contribute to the reduced exercise tolerance and dyspnoea on exercise. The j-receptors are stimulated by pulmonary increased pressure and fluid, eg with heart failure and pulmonary embolism.

A further set of receptors has recently been found to be relevant in situations of chronic dyspnoea, namely the ergoreceptors (or metaboreceptors).[7] These detect lactate and other metabolic by-products and can provoke breathlessness on minimal exertion. They are probably upregulated in the presence of deconditioning, eg when patients become more immobile with advancing disease.

#### 4.1.3. *Integration of respiratory control and dyspnoea expression*

Recent neuro-vascular imaging techniques such as PET and functional MRI have shed light on how respiration is controlled in conscious and subconscious parts of the brain.[5,8] Afferent signals from chest and diaphragm muscles pass to the medulla, thence to the thalamus and terminate in the somatosensory cortex. It is thought that this pathway may mediate the sensory or intensity component of dyspnoea. Signals from the airways and lungs are also transmitted via vagal inputs to the medulla, but relay thence to the amygdala, thalamus, insula and cingulate cortex. This pathway is thought to be directed towards the affective or unpleasantness component of dyspnoea awareness. Both pathways project finally to the motor cortex where descending signals originate down to brainstem and respiratory muscles.

Experimentally-induced air hunger is correlated with increased blood flow in the mesencephalic and hypothalamic areas; limbic and paralimbic areas (amygdala); motor areas and insula; and cerebellum.[8]

The medullary respiratory centre which coordinates normal respiration and the response to disease and circulating chemicals is actually a complex set of structures including the ventral and dorsal respiratory groups, pneumotaxic centre and the pre-Botzinger complex. The latter is probably the centre where respiratory rhythm originates. It is rich in neurones which are sensitive to opioids, GABA, serotonin and other neurotransmitters.[9]

Opioid receptors in these areas are involved intimately in the regulation of breathing and also in the sensation of dyspnoea. They mediate the ventilatory response to varying $CO_2$ tension. Therapeutic opioid drugs initially cause dose-related depression of ventilatory frequency (bradypnoea) with an accompanying increase in tidal volume. With higher doses, minute volume falls, leading to hypoventilation and hypercapnia. Recent studies have demonstrated that when opioids are used carefully and titrated against the level of dyspnoea, even when respiratory rate falls there is – at least initially - no significant ventilatory compromise.[10] The danger arises when opioid drugs are given in excessive doses in comparison to the patient's needs or are being abused, and there is then a risk of compounding reduced ventilation with blunting of hypercapnic ventilatory drive, with the consequence of acute hypercapnic respiratory failure (for therapeutic consequences see below).

#### 4.1.4. *Other factors*

There is a clear relationship between breathlessness and anxiety. Identification of cerebral pathways has begun to clarify how the sensory and affective dimensions of, and triggers for, dyspnoea can be important for some patients.[5,6,11] As cancer, COPD and heart failure often arise in older people, it is relevant to consider the effects of ageing on respiratory functioning and the sensation of breathlessness. These include – decrease in lung elasticity and respiratory muscle strength leading to reduction in forced vital capacity; increased air-trapping and impairment of gas exchange; attenuated ventilatory response to hypoxia and hypercapnia but increased ventilatory response to exercise.

Recent advances in understanding the nature of cachexia, which occurs in many patients with advancing cancer, have identified failing chest wall and diaphragmatic muscle strength as additional factors in the pathogenesis of dyspnoea. It has been shown that TNF-alpha can depress diaphragm muscle fibre contractility force directly.[12]

## 5. Patient experience

Episodes of breathlessness can be very frightening, as many patients feel as if they are drowning or choking to death.[11] Thus, the fear of inducing breathlessness may lead the patient to restrict physical activity with the consequence of becoming chair- or bed-bound, which in turn leads to generalised muscle deconditioning. This can be a factor in the generation of the ergoreceptor response, with even more likelihood of inducing breathlessness when the patient does have to mobilise.

Qualitative studies have shown that breathless patients can in fact separate three dimensions of the symptom –

1. Air hunger (unpleasant sensation of the need to breathe, while being unable to increase ventilation)
2. Effort of breathing (physical discomfort and tiredness associated with breathing)
3. Chest tightness (feeling of constriction and inability to breathe in and out)

There are some indications that different disease processes may increase selectively one or other of these dimensions, but they cannot be used for diagnostic purposes.

## 6. Diagnostic tests

It is important to distinguish dyspnoea clinically from other types of abnormal breathing pattern, especially tachypnoea associated with increased metabolic rate such as with fever; air hunger associated with metabolic acidosis, eg diabetic ketosis; hyperventilation associated with panic disorders; Cheyne-Stoke respiration when breathing can appear to be increased and laboured, alternating with periods of hypopnoea or even apnoea.

It is helpful to ask the patient to rate the severity of breathlessness using a recordable scale. This can establish a baseline and help to monitor response to interventions. Most patients with normal cognitive function can describe the symptom verbally (mild-moderate-severe) or numerically (0-10, where 10 is the worst shortness of breath experienced). Visual analogue scales (VAS) are best reserved for research. The Cancer Dyspnoea Scale has been designed specifically for use in clinical studies and covers the three dimensions of sense of effort, sense of anxiety and sense of discomfort.[13]

Sometimes the history is helpful in making a differential diagnosis – eg, relationship to exercise; position (eg orthopnoea with heart failure); paroxysmal dyspnoea with palpitation and fainting, eg with pulmonary embolism. Usually, physical examination and investigations are also needed to make a definitive diagnosis. Important features of the examination include looking for anaemia, central cyanosis, signs of heart failure, bronchospasm, pulmonary consolidation and pleural effusion.

Unless the patient is *in extremis*, it is advisable to investigate the patient to look for pathological and treatable causes. A list of the useful tests is given in Table 3. Some of these can also be used for monitoring progress.

A rapid, bedside test which is often helpful clinically is pulse oximetry. The doctor should be aware of the situations when oximetry is less reliable and then a corroborative test of arterial blood gases should be sought.[14] This is particularly important when drug-induced respiratory depression is suspected and there is a possibility of administering an antagonist, eg naloxone.

**Table 3 – Useful tests in managing dyspnoea of cancer**

| Type | Specific test |
|---|---|
| Imaging | Chest X-ray<br>CT scan<br>Ultrasound scan (eg for pleural or pericardial effusion)<br>CT-PA or V/Q scan – for pulmonary embolism |
| Blood tests | Hb<br>$SaO_2$ for oxygenation<br>Arterial blood gases for respiratory failure |
| Functional | Pulmonary function tests ($FEV_1$, FVC to diagnose small airways obstruction)<br>Flow volume loop to diagnose upper airways obstruction;<br>$TL_{CO}$ or $K_{CO}$ to assess gas exchange<br>Exercise test (6 minute walk; shuttle walking test) – for research |

When a patient presents to the emergency department with acute severe breathlessness, there is usually not time to perform all these investigations before embarking on corrective or symptomatic (palliative) treatments. The minimal tests in this situation are – blood pressure; pulse oximetry; ECG; chest X-ray. If pulmonary embolism is suspected, eg there is recent painful leg swelling, then an urgent CT-PA and peripheral blood flow tests are justified.

The patient should be kept informed and reassured while these tests are being done and symptomatic treatment should be instituted immediately, even when the underlying cause is not clear. It is not acceptable to leave a patient who is moderately or severely breathless without explanation and some form of palliation. On the other hand, the blanket use of supplementary oxygen – often initiated as 'something to do' - is not recommended, especially if the $SaO_2$ is over 95%.

## 7. Management

The management plan should ideally be directed to relieve or eliminate the underlying cause of the breathlessness- including co-morbid conditions - wherever this is feasible. Thus, consideration should be given to bronchodilator and possibly steroid therapy for exacerbations of airways disease; correction of anaemia; and antibiotics for bronchitis or pneumonia. It is important not to add to the patient's burden, eg by fluid overload or inappropriate use of intravenous antibiotics in a terminally ill person.

### 7.1. *Tumour-directed treatment*

Oncologists will be aware of the role of anti-cancer treatments for palliating respiratory symptoms. In lung cancer, both chemotherapy and radiation therapy can reduce dyspnoea but the response rates are variable and often less than those for palliating cough and haemoptysis.(Tables 4 and 5).[3] Endobronchial therapies such as stenting, brachytherapy and laser may be helpful for selected cases, but the research evidence from randomised controlled trials is poor.[15,16] Upper airway stents can be very helpful in cases of tracheal compression producing stridor. Patients with suspected or proven lymphangitis carcinomatosa - which can cause extreme breathlessness, panic and fatigue – can be started on medium dose corticosteroid (dexamethasone 16 mg per day) while waiting for anti-cancer treatment to take effect. The steroid should be tapered down after 5-7 days.

### 7.2. *Pleural and pericardial effusions*

Pleural effusions often cause rapidly increasing and very distressing dyspnoea, which need urgent paracentesis, preferably in an ambulatory setting using a pig-tail catheter.[17] After the initial drainage, some patients may need no further intervention, but effusions often recur. Pleurodesis is usually helpful in these recurrent cases after lung re-expansion, using talc or tetracycline. Only rarely is an open or VATS pleurecetomy required. A new approach is the use of longer term tunnelled in-dwelling pleural catheters (Pleur-X) with vacuum bottles,

**Table 4 – Responses of respiratory symptoms in NSCLC to radiotherapy**

| Dose | Study | Cough (%) | Haemoptysis (%) | Dyspnea (%) |
|---|---|---|---|---|
| Radical (curative)-60 Gy | Langendijk et al. | 31 | 83 | 37 |
| Convenlional palliation | Langendijk et al. | 49 | 79 | 3 |
| Hypofractionated-17 Gy | MRC 1997 | 48 | 95 | 46 |
| Hypofractionated -17 Gy | Plantaniolis et al. | 24 | 6 | 55 |
| Hypofractionated -20 Gy | Bhatt et al. | 63 | 77 | 42 |

Table adapted from Ahmedzai SH. Cough in cancer patients. Pulm Pharmacol Therap. 2004; 17:415-423 (Ref3).
Summary of the results of radiotherapy for palliation of respiratory symptoms in NCSLC (figures quoted are response rates for each symptom)

**Table 5 – Responses of respiratory symptoms in NSCLC to chemotherapy**

| Regimen | Study | Cough (%) | Haemoptysis(%) | Dyspnoea (%) |
|---|---|---|---|---|
| Cisplatin/vindesine + mitomycin or ifosfamide | Fernandez et al | 45 | 91 | 78 |
| Mitomycin/ifsosfamide/cisplatin | Cullen et al | 70 | 92 | 46 |
| Gemcitabine alone | Thatcher et al | 44 | 63 | 26 |
| Gemcitabine/cisplatin | Jassem et al | 44 | 75 | 36 |
| Gemcitabine alone | Vansteenkiste et al | 42 | 69 | 39 |
| Cisplain + vindesine | Vansteenkiste et al | 50 | 59 | 38 |

Table adapted from Ahmedzai SH. Cough in cancer patients. Pulm Pharmacol Therap. 2004; 17:415-423 (Ref[3]).
Summary of the results of chemotherapy for palliation of respiratory symptoms in NCSL (figures quoted are response rates for each symptom).

which can allow patients to continue drainage after returning home.[18] Pericardial effusions are usually associated with severe dyspnoea and a poor prognosis, but surgical drainage can often allow temporary relief until other measures are started.

### 7.3. *Drug management*

After trying disease-specific drugs treatments (bronchodilators, diuretics etc), it is essential to initiate symptomatic treatment without delay if the patient has not responded. The main classes of symptomatic (ie palliative) drug treatments for breathlessness are benzodiazepines and opioids.

#### 7.3.1. *Benzodiazepines*

Benzodiazepines work by activating the inhibitory GABA pathways and are useful if there is a significant component of anxiety associated with the dyspnoea and especially when panic attacks occur in anticipation of activity (see Table 6). Shorter acting drugs, such as lorazepam, are preferred, as patients can also be taught to take this (0.5 mg tablet) sublingually to minimise anxiety attacks. For patients who are experiencing severe breathless episodes, eg with terminal disease from upper airways obstruction, lymphangitis or pericardial tamponade, subcutaneous injections or a continuous sc infusion of midazolam are very helpful. The dose should be started at 2.5 mg stat and gradually titrated upwards, daily or more frequently, to reduce panic without causing undue sedation. Diazepam should not be used because of its prolonged half-life. Although there is no evidence that benzodiazepines modify the sensation of dyspnoea *per se*, as there is with opioids (see below), there is evidence that the combination of benzodiazepine with opioid may be better than either class alone.[19]

**Table 6 – Action of main drug classes used in treating dyspnoea**

| | Drug class | | |
|---|---|---|---|
| Pharmacological action | Opioid | Benzodiazepine | Nebulised furosemide[a] |
| Relieves dyspnoea at cerebral level | ✓ | ? | × |
| Reduces ventilatory response to hypercapnia | ✓ | ✓ | × |
| Reduces anxiety | ✓ | ✓ | × |
| Causes sedation | ✓ | ✓ | × |
| Relieves pain | ✓ | ? | × |
| Reduces cough | ✓ | × | × |
| Reduces cardiac pre-load | ✓ | × | ? |
| Reduces cardiac after-load | × | × | ? |
| Reduces afferent signalling from lungs | ? | × | ✓ |

a NB. Use of nebulised furosemide is based on small studies – still experimental

#### 7.3.2. *Opioids*

There is good research evidence from volunteer and clinical studies that opioid drugs can relieve the sensation of breathlessness and also bring many other subjective and objective benefits (see Table 6). Additionally, opioids can reduce pain which may be contributing to the restriction of chest wall or diaphragmatic movements. In left ventricular failure, opioids can off-load the heart and thus improve oxygen consumption. The useful opioid drugs are morphine and its synthetic analogues such as hydromorphone or oxycodone. (In the UK diamorphine is used parenterally but there is no advantage to this drug other than its greater water solubility.) For the 'opioid-naïve' the dose should be started at 5 mg orally or 2.5 mg sc, repeated 2-4 hourly as necessary, being titrated up on a daily basis until the patient is settled, or experiences unacceptable side-effects. Several studies and a Cochrane systematic review have shown the benefit of opioids in managing the breathlessness of cancer, COPD and heart failure.[20,21]

For patients who are already on opioids for pain control, it is reasonable to offer 'as required' doses of 25-50% greater, than might already be being used for breakthrough pain. For both naïve and opioid-tolerant patients, regular long-term treatment is associated with troublesome adverse effects – notably constipation and sedation.[22] For this reason, and also because for many patients dyspnoea is episodic and often predictable, 'as required' dosing for dyspnoea may be as good as regular dosing.

Although there are opioid receptors in the airways, there is no convincing evidence that these mediate the sensation of dyspnoea. A systematic review has found no benefit of nebulised opioids for this symptom.[20]

In spite of the good evidence in favour of using opioids for dyspnoea, many patients are denied their benefit because their clinicians are afraid of a potentially serious adverse effect: respiratory depression. We know that the sensation of breathlessness is mediated, at least in part, by opioid receptors in cortical centres and amygdala. It is has been shown that lower doses of opioids, used judiciously by careful titration against symptom level rather than by indiscriminate dose increments, can reduce the sensation without initiating hypercapnic ventilatory depression that is mediated via the medullary centre.[10]

Even when used carefully, opioids do reduce respiratory rate, although tidal volume is maintained or increased so that minute ventilation does not suffer until the dose is increased excessively.[23] Thus, a reduced respiratory rate *per se* is not an indication of dangerous opioid toxicity in this situation. Only if $SaO_2$ falls to <90% (depending on age and previous respiratory disease) and if there is accompanying evidence of raised $P_aCO_2$ on arterial blood gases or if the patient becomes unrousable, is it justified to reverse the opioid with naloxone. Even if opioid reversal is necessary because of significant respiratory depression, the doctor performing it should be aware that it may provoke a sudden increase in dyspnoea and especially pain, if the patient were previously taking the drug for these symptoms. There should, therefore, be a plan of how to re-instate opioids at a lower dose, using shorter acting formulations, to allow for a quick and controlled restitution to a safe level.

Recent studies have suggested that the synthetic opioid buprenorphine, which has complex pharmacological activity against several opioid receptors, may be safer in this situation. It appears that buprenorphine has an effective ceiling dose for respiratory depression, which is lower than its ceiling dose for pain.[24]

#### 7.3.3. *Nebulised furosemide*

In contrast to the lack of effect with nebulised opioids, the inhalation of furosemide has been shown in several small, single-dose studies to result in bronchodilatation and reduction of breathlessness.[25–27] The effective dose is from 20-40 mg, which on systemic absorption is too low to cause significant diuresis. The mechanism of action of nebulised furosemide is thought to be stimulation of lung airways stretch receptors and parencyhmal j-receptors, which modulates afferent signalling to the brain. As this appears to be effective and free of adverse effects, further large randomised trials, using repeated doses, are warranted.

### 7.4. *Gas and airflow therapy*

Patients who have significant (<90%) de-saturation at rest or on exertion should be offered a trial of oxygen. To maintain speech communication and reduce dry mouth, this is best delivered by nasal cannulae, unless high flow rates are required. There is little evidence for giving supplementary oxygen unless the patient desaturates to below 90%, or is very anaemic. Too liberal use of oxygen can make the patient dependent on this modality.[28] All doctors should be aware that it is dangerous to give too high a flow rate of oxygen to a patient with advanced COPD who may be at risk of hypercapnic respiratory failure. In severe dyspnoea associated with cancer, a mixture of helium with oxygen ('heliox') can give quicker and greater relief of dyspnoea than oxygen alone, owing to the improved flow characteristics of helium gas.[29]

Part of the benefit of 'oxygen' therapy is probably derived from the increased airflow of cool compressed gas past the nose, mouth and anterior part of the face. Passing cold air alone over these areas can reduce the sensation of breathlessness.[30] It is therefore helpful to provide the patient with a bedside fan and to allow air circulation by opening windows, if possible.

### 7.5. *Non-medical approaches*

Because of the troublesome side-effects (and costs) of drug or oxygen therapy, it is helpful to offer the patient non-medical approaches to palliate dyspnoea. Some patients respond well to structured relaxation training, usually with the help of a pre-recorded tape with comforting words and music. Other helpful techniques include breathing control, exploring coping strategies, pacing and goal-setting.[31] Acupuncture has not been shown consistently to have value for this symptom.

## 8. Terminally ill patients

At the very end of life, dyspnoea often becomes more severe and refractory to previously helpful drug and non-drug thera-

pies.[32] As the patient becomes unable to take oral medication, it is often helpful to initiate subcutaneous medication, consisting of bolus injections of an opioid and midazolam. Patients who need more than two doses of these per day should be started on a continuous subcutaneous infusion. Midazolam can be combined in a syringe driver with morphine, hydromorphone or oxycodone. With significant renal impairment, alfentanil is the best choice for opioid, however it is often sufficient in patients close to death simply to reduce the dose and frequency of the opioid they have been taking. Doses of all drugs should be monitored daily and decreased as well as increased as necessary. The aim is to reduce the patient's reports or apparent distress from dyspnoea, not usually to induce sedation.

Under specialist care, the technique of 'palliative sedation' is sometimes used for extremely refractory symptoms and very agitated patients who are actively dying. In a Japanese series of 102 cancer patients, dyspnoea was the second most common intractable symptom after fatigue for initiating this (41% and 44%, respectively).[33] Palliative sedation should be used as a last resort and only by trained palliative care professionals. It is not a therapeutic option for patients who are not close to death.

The dying patient may have noisy breathing ('death rattle') which is due to air passing over retained mucus secretions in the upper airways. The use of an intermittent or continuous anticholinergic such as hyoscine butylbromide or glycopyrronium, together with gentle pharyngeal suction and positioning of the patient, can reduce or abolish these sounds.[34]

## 9. Future research

Although there has been significant progress made in recent years in our understanding of respiratory control and the pathogenesis of dyspnoea, we are still lagging behind in having evidence-based methods for its relief, in comparison to cancer pain. There are several areas of cancer-related dyspnoea which would benefit from increased research in the form of multicentre studies and especially randomised controlled trials. These include:

- Clarifying the optimum choice of opioids and benzodiazepines and their regimens (routes, dosage, combinations) to use in palliating dyspnoea
- Elucidating the mechanism of nebulised furosemide and understanding how to use it
- Proving the value of interventional techniques such as endobronchial therapies and pleurectomy for refractory patients
- Understanding how best to use non-medical approaches alongside medical management
- Clarifying the role and techniques for palliative sedation in end-stage refractory dyspnoea.

## Conflict of interest statement

None declared.

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