Clinical management of dyspnoea

Jay R Thomas and Charles F von Gunten

Dyspnoea, defined as a sensation of an uncomfortable awareness of breathing, is one of the most frightening and distressing symptoms for patients with cancer. It is very common in cancer patients with and without direct lung involvement. The gold standard of diagnosis and assessment is the patient’s self-report. Measurements of respiratory rate, oxygen saturation, and arterial blood gases do not measure dyspnoea. Fast, safe, and effective relief of the symptom is possible whether or not identifiable reversible causes exist. Opioids are the first line of therapy for such relief. Medical management can be directed at the underlying cause when the potential benefits outweigh the burdens of such treatment. In rare cases for which symptomatic treatment does not control dyspnoea to the patient’s satisfaction, sedation is an effective, ethical option.


Dyspnoea is defined as an uncomfortable sensation or awareness of breathing. The reported frequency in cancer patients varies from 21% to 90%, depending on the stage of cancer. The symptom is particularly common among patients who have primary or metastatic involvement of the lung. However, for reasons that are not entirely clear, it is also common in patients with no direct lung involvement. The National Hospice Study found that 24% of patients with dyspnoea had no known cardiopulmonary pathology. Moreover, cancer is commonly diagnosed in patients who have significant underlying cardiopulmonary problems, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure.

Pathophysiology of dyspnoea

The pathophysiology of dyspnoea is incompletely understood. Most data come from studies of healthy volunteers with experimentally induced dyspnoea or from patients with COPD. Dudgeon and Lertzman undertook a prospective analysis of 100 patients with dyspnoea and advanced cancer in an attempt to elucidate the causes. They found that 49% had lung cancer; 65% had lung or pleural involvement; 40% were hypoxaemic with oxygen saturation of less than 90%; 12% had arterial carbon dioxide partial pressures (PaCO₂) of 6·0 kPa or higher; 52% had a component of bronchospasm; 29% had evidence of cardiac ischaemia, congestive heart failure, or atrial fibrillation; and 20% were anaemic with a haemoglobin concentration of less than 10 g/dL. Pulmonary function tests showed that 5% had an obstructive pattern, 41% a restrictive pattern, and 47% mixed obstructive/restrictive pattern. The median maximum inspiratory pressure was -16 cm water (a normal reading equates to a negative pressure of at least -50 cm water), indicating significant respiratory muscle weakness. None of these patients had received chemotherapy linked to pulmonary disease, and 40% had had radiotherapy that included at least a portion of the lungs. The average number of potential causes of dyspnoea per patient was five. Although the study was small, limiting the extent to which the results can be generalised, it implies that the cause of dyspnoea is multifactorial in many cancer patients.

To understand how these clinical states may trigger dyspnoea, one must first understand how respiratory sensory information is processed by the brain and leads to respiratory activity (figure 1). The respiratory centre in the medulla and pons coordinates the activity of the diaphragm, the intercostal muscles, and the accessory muscles of respiration. It receives sensory information from central and peripheral chemoreceptors, peripheral mechanoreceptors from muscles, tendons, and joints, and pulmonary vagal afferents. The vagal afferents include pulmonary stretch receptors that are activated by lung inflation, pulmonary irritant receptors triggered by air flow and smooth-muscle tone, and alveolar C fibres that respond to pulmonary interstitial and capillary pressure. The afferents may also send information directly to...
the cerebral cortex, which is thought to integrate this sensory input with other cognitive and emotional factors and motor information from the respiratory centre to create the perception of breathing. With the advent of functional brain imaging by positron emission tomography (PET), researchers may have identified cortical areas involved in the perception and modulation of dyspnoea.29 These studies implicate areas such as the anterior insula and the posterior cingulate gyrus.

To simplify conceptualisation of the pathophysiology of dyspnoea, three important components can be independently discerned.

**Work of breathing** – The increased effort required for breathing against increased resistance (e.g., COPD) or breathing with weakened muscles (e.g., neuromuscular disease or cachexia) is sensed as dyspnoea. Most studies point to increased respiratory work as an important component of dyspnoea.

**Chemical** – Medullary chemoreceptors predominantly sense hypercapnia. Carotid and aortic chemoreceptors predominantly sense hypoxaemia. These sensations can lead to dyspnoea in a way that is independent of increased respiratory effort.30 Despite common belief, hypoxaemia seems to have a less significant role than hypercapnia in dyspnoea. First, moderately severe hypoxaemia is needed to trigger the peripheral chemoreceptors.31 Second, the compensatory increase in ventilation triggered by hypoxaemia drives down the carbon dioxide concentration, which then partly counteracts the effect of the hypoxaemia. Finally, most patients with cancer and dyspnoea are not hypoxaemic.

**Neuromechanical dissociation** – O’Donnell and Webb proposed that when there is a mismatch between what the brain desires for respiration and the sensory feedback it receives, dyspnoea is increased.32 For example, when researchers limit the inspiratory flow rate at which a person is allowed to breathe, dyspnoea results despite there being no change in respiratory work or chemical status.

Therefore, the pathophysiology of dyspnoea must be understood to be multifactorial.

**Diagnosis**

The gold standard for diagnosis of dyspnoea is the patient’s self-report. There is no other reliable, objective measure of the disorder. Measurements of respiratory rate, oxygen saturation, and arterial blood gases are not correlated with and do not measure dyspnoea. For example, patients may be hypoxaemic but not dyspnoeic, or dyspnoeic but not hypoxaemic.

In the clinical research setting, dyspnoea can be measured in several ways. Functional assessment tools such as the shuttle walking test14 and the reading aloud of numbers15 have been validated. When functional assessment is difficult or when perceptions are targeted, scales such as the visual analogue and Borg17 scales can be used. These validated measures are simple and reproducible. Visual analogue scales typically have a 100 mm line with verbal descriptors such as “no breathlessness” and “worst possible breathlessness” at the ends. The patient makes a mark on this line corresponding to the extent of his or her dyspnoea. The modified Borg scale is a 10-point scale with descriptors at the ends of the scale and specific numbers within it. Absolute answers promote better comparison between individuals. In clinical practice, such measurement scales have limits. Some patients have trouble making the abstract connection between a scale and their sensation of dyspnoea.

A thorough assessment should precede clinical management of dyspnoea. The history and physical examination are essential elements. Medical, smoking, and occupational histories and previous radiotherapy or chemotherapy may provide important diagnostic clues. Since cognitive and emotional factors can modify dyspnoea, an understanding of a patient’s psychosocial and spiritual stressors may be necessary also. A physical examination in conjunction with simple studies such as pulse oximetry, complete blood count, and a chest radiograph are sufficient in most cases to clarify an understanding of the pertinent pathophysiology. When the possible benefits of further investigation exceed the burdens, additional studies may include arterial blood gas measurements, pulmonary function tests, computed tomography, echocardiography, and ventilation-perfusion scans. Possible specific causes of dyspnoea are listed in panel 1.

**Symptomatic management**

The therapeutic goal of symptomatic management of dyspnoea is to relieve the patient’s sense of the effort of breathing. This aim can be achieved by pursuing one or more strategies, including both pharmacological and non-pharmacological interventions. The strategies need not be limited to patients for whom efforts to relieve the underlying causes are thought to be futile or excessively onerous.

**Opioids**

Opioids are the first line of therapy for symptomatic control of dyspnoea. Opioids decrease exercise-induced dyspnoea and increase exercise tolerance in patients with COPD.34,35 Bruera and colleagues were the first to carry out a study in cancer patients.36 In their placebo-controlled crossover study, opioids relieved dyspnoea without evidence of respiratory depression. There was no change in respiratory rate or oxygen saturation. Mazzocato and co-workers showed that in opioid-naïve patients, as little as 5 mg morphine sulphate delivered subcutaneously was effective in controlling dyspnoea.37 The duration of the effect was consistent with the serum half-life of morphine and equivalent to that observed for pain relief, about 4 h. For patients on baseline opioids, Allard and colleagues found that a 25% increase in the baseline dose provided breakthrough relief of dyspnoea for up to 4 h.22 A typical opioid regimen to control chronic dyspnoea includes both a sustained-release opioid for baseline control and an immediate-release opioid for breakthrough dyspnoea.

The mechanism by which opioids relieve dyspnoea is not well understood. Systemic administration of naloxone, an opioid antagonist, increases dyspnoea; this finding supports the part that endogenous opioids play in controlling dyspnoea.38 Opioid receptors are located throughout the...
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Peripherally acting opioids, for example morphine, have been shown to improve dyspnoea in uncontrolled trials and anecdotally. The clinical role for the opioid receptors in the lung was thus inferred. However, several clinical studies of nebulised opioids have not shown this effect; thus, the role of pulmonary opioid receptors remains in dispute.

Although their mechanism of action is not entirely clear, opioids are safe and effective for the relief of dyspnoea when prescribed according to the guidelines outlined in panel 2. These recommendations include patients with compromised pulmonary status such as those with COPD. Light and colleagues studied 13 patients with COPD whose average forced expiratory volume in 1 s (FEV1) was 0.99 L, PaCO2 less than 6.1 kPa, and arterial partial pressure of oxygen (PaO2) more than 7.3 kPa. The patients were given an oral morphine dose of 0.8 mg/kg before exercise. An opioid-naive patient weighing 70 kg would have received 56 mg morphine in this study. This dose is many times larger than a typically patient weighing 70 kg would have received 56 mg morphine. Although patients had a trend towards improvement on a subscale for dyspnoea on morphine, it was not significant. Nevertheless, nine of 14 patients who completed the study chose to continue morphine afterwards; one of these had a significant improvement in exercise tolerance and a decrease in dyspnoea. Thus, further clinical studies are needed to optimise opioid therapy. However, that study showed that long-term opioid treatment was safe in terms of respiratory depression in a population of patients with severe COPD and an average FEV1 of 0.6 L.

Untreated opioid side-effects, such as constipation, lethargy, and nausea, can affect quality of life.

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Panel 1. Causes of dyspnoea

<table>
<thead>
<tr>
<th>Directly related to cancer</th>
<th>Indirectly related to cancer</th>
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<tbody>
<tr>
<td>Primary/metastatic parenchymal lung involvement</td>
<td>Pneumonia</td>
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<td>Airway obstruction (intrinsic or extrinsic tumour)</td>
<td>Cachexia</td>
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<td>Carcinomatous lymphangitis</td>
<td>Anaemia</td>
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<td>Pleural tumour</td>
<td>Electrolyte abnormalities</td>
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<td>Malignant pleural effusion</td>
<td>Pulmonary embolus</td>
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<td>Pericardial effusion</td>
<td>Paraneoplastic syndromes</td>
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<td>Superior vena cava syndrome</td>
<td>Acites</td>
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<td>Tumour microembol</td>
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<td>Phrenic nerve paralys</td>
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<td>Atelectasis</td>
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<tr>
<td>Trachea-esophageal fistula</td>
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<tr>
<td>Chest-wall invasion (carcinoma en cuirasse)</td>
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<tr>
<td>Pathological chest-wall fractures</td>
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Panel 2. Opioid therapy

**Opioid-naive patients with mild dyspnoea**

- Hydrocodone 5 mg orally every 4 h
- Codeine 30 mg orally every 4 h
- Morphine sulphate 5 mg orally every 4 h
- Oxycodone 5 mg orally every 4 h
- Hydromorphone 1 mg orally every 4 h

For breakthrough symptom management, give an equivalent dose every 1–2 h as needed.

**Opioid-naive patients with severe dyspnoea**

- Morphine 5 mg orally every 4 h
- Oxycodone 5 mg orally every 4 h
- Hydromorphone 1 mg orally every 4 h

For breakthrough symptom management, give an equivalent dose every 1–2 h as needed. Titrate in increments of 50–100% every 24 h as needed.

**Opioid-tolerant patients**

Increase baseline opioid dose by 25–50% and titrate as above.

Dyspnoea

Related to cancer therapy

- Surgery (after lobectomy or pneumonectomy)
- Radiation pneumonitis
- Chemotherapy-induced pulmonary fibrosis
- Chemotherapy-induced cardiomyopathy

Unrelated to cancer

- Chronic obstructive pulmonary disease
- Asthma
- Congestive heart failure
- Cardiac ischaemia
- Arrhythmias
- Pulmonary vascular disease
- Obesity
- Neuromuscular disorders
- Asthma
- Anxiety
- Pneumothorax
- Interstitial lung disease
- Psychosocial/spiritual pain

Treatment options are:

- Morphine 5 mg orally every 4 h
- Oxycodone 5 mg orally every 4 h
- Hydromorphone 1 mg orally every 4 h

For breakthrough symptom management, give an equivalent dose every 1–2 h as needed. Titrate in increments of 50–100% every 24 h as needed.

For patients with severe pulmonary disease such as COPD, start at 50% of the above doses and titrate more conservatively with increments of 25% every 24 h as needed.

**Opioid-tolerant patients**

Increase baseline opioid dose by 25–50% and titrate as above.
patients become pharmacologically tolerant to the adverse effects of opioids, except for constipation, within 1–2 weeks.\textsuperscript{28} If needed, stimulants (for example, methylphenidate) and antidopaminergic antiemetics (such as prochlorperazine) can be prescribed to control adverse effects for the short term. For constipation, all patients on opioids should be on an effective bowel regimen, typically consisting of both a stool softener and a stimulant laxative. With time and appropriate symptom management, opioid side-effects can be successfully surmounted in most cases.

**Anxiolytics**

The role of anxiety in dyspnoea remains unclear. Many patients report anxiety concurrent with the feeling of breathlessness. Dyspnoea can lead to anxiety, and anxiety can exacerbate dyspnoea. Opioids alone may break the cycle by relieving dyspnoea. Although the opioids may initially have anxiolytic properties, patients typically become tolerant to these effects. Therefore, anxiolytic properties alone are unlikely to explain the effect of opioids on dyspnoea.

Anxiolytics (such as benzodiazepines) are commonly prescribed for anxiety related to dyspnoea. However, the evidence for their effectiveness is not very persuasive. Mitchell-Heggs and colleagues’ placebo-controlled single-blind study of four patients with COPD showed that moderate doses of diazepam improved dyspnoea.\textsuperscript{29} However, subsequent double-blind studies of diazepam or alprazolam in healthy volunteers or patients with COPD showed no benefit over placebo.\textsuperscript{30–32} Dudgeon and Lertzman\textsuperscript{4} found that anxiety was correlated with dyspnoea, but in their multivariate model, it was sufficient to explain only 10% of the variance of dyspnoea.

These data support the conclusion that benzodiazepines alone should not be first-line therapy for dyspnoea. Relief of the symptom by other means such as opioids may be sufficient to remove the source of anxiety. However, treatment of anxiety does have a role in a subset of patients for whom it is a prominent component of the distress. For these patients, benzodiazepines can be safely prescribed at appropriate doses (panel 3), prescribed in conjunction with opioids without fear of respiratory depression when guidelines are followed. The tranquiliser chlorpromazine\textsuperscript{33} and buspirone,\textsuperscript{34} a non-benzodiazepine anxiolytic, have been reported to decrease dyspnoea.

**Oxygen**

Oxygen can reverse hypoxaemia. If this feature is the cause of dyspnoea, oxygen may be the only therapy required. However, the perceived benefit in patients with cancer who are dyspnoeic far exceeds the number who have hypoxaemia.

There have been only a few small studies assessing oxygen therapy for hypoxaemia in patients with cancer. One randomised, double-blind cross-over study showed that oxygen improved dyspnoea in these patients,\textsuperscript{35} but another controlled study showed no advantage of oxygen over compressed air.\textsuperscript{36} As mentioned earlier, hypoxaemia may be a weak stimulus of dyspnoea. Many patients are dyspnoeic but not hypoxaemic; PaO\textsubscript{2} is not related to subjectively reported dyspnoea. Some patients have noted improvement in dyspnoea with oxygen despite unrelieved hypoxaemia.

Although there is probably a placebo effect of oxygen and the medical symbolism inherent in its administration, there may be other explanations for its effectiveness. Cool air blowing on the face (such as from sitting in a breeze or in front of a fan) reduces dyspnoea. Several studies support the hypothesis that stimulation of the trigeminal nerve (V2 branch) has central inhibitory effects on dyspnoea.\textsuperscript{37–39} Thus, part of oxygen’s effect may be due to this sensory stimulation rather than correction of hypoxaemia or a pure placebo effect. Thus, cool, moving air is a possible option for all dyspnoeic patients.

Many clinicians will consider a trial of oxygen therapy in all dyspnoeic patients. However, there are burdens associated with oxygen therapy. It is costly and cumbersome. For many patients, it unnecessarily restricts mobility and alters self-image. In addition, clinicians may not explore the other symptomatic therapies that can render the patient comfortable and less dependent on the equipment needed for oxygen therapy.

**Cognitive/behavioural interventions**

Dyspnoea also has cognitive and emotional components. Bredin and colleagues assessed the effect of a nurse-run dyspnoea clinic in a multicentre, randomised, controlled study.\textsuperscript{40} The concept is similar to pulmonary rehabilitation clinics for COPD. The intervention group were taught breathing control, activity pacing, and relaxation techniques, and were given psychosocial support. Compared with controls, the patients who underwent the intervention showed improvement in dyspnoea scores, performance status, and emotional states. Thus, non-pharmacological therapies have a role in the control of dyspnoea.

Advice to the clinician managing a patient with dyspnoea is also in order. A calm, confident demeanour is reassuring to the patient and family and helps to diminish the anxiety component. By contrast, the clinician who responds anxiously to the frightened, worried, dyspnoeic patient is likely to have the opposite of a therapeutic effect.

**Management of underlying causes**

Both the degree of diagnostic investigation and the choice of interventions must be guided by the patient’s goals and the extent of disease. The patient’s functional status and prognosis are important factors to consider. After risk/benefit analysis, treatment should be directed at reversible causes when possible, without neglecting concurrent symptomatic treatment.
Dyspnoea directly related to the cancer can potentially be treated with resection, chemotherapy, or radiotherapy. Obstruction can be treated locally with laser therapy, cryotherapy, or stenting. Malignant pleural effusions can be drained by thoracocentesis, and if they recur, pleurodesis may be attempted. Fluid drainage may improve the mechanical advantage of the respiratory muscles to relieve dyspnoea.\(^4\)

Red-blood-cell transfusion remains controversial. Studies have shown qualitative improvement in symptoms, but there has been no clear correlation with pretransfusion haemoglobin concentrations.\(^5\) Therefore, transfusion therapy needs to be individualised. For anaemia-related dyspnoea, erythropoietin is slowly effective and avoids the risks of transfusion but requires time (months) and is expensive.

Glucocorticoids may be useful in bronchospasm, superior vena cava syndrome, carcinomatous lymphangitis, and radiation pneumonitis. Antibiotics may be appropriate for infections. Anticoagulants can prevent and treat thrombotic pulmonary emboli.

Bronchodilators such as salbutamol and ipratropium treat reversible bronchospasm. The stereoisomers of the selective β-agonist albuterol have lately been isolated for clinical studies. The S-isomer seems to be proinflammatory so a purified R-isomer (levalbuterol) has been introduced clinically. Similarly, studies in asthma indicate that the R-isomer can induce bronchodilation at a lower concentration than racemic albuterol and consequently has fewer β-adrenergic side-effects.\(^6\) Methylxanthines may have a role in bronchodilation as well as improving diaphragmatic contractility in highly selected patients. Although clinical studies have not addressed this issue, improved contractility may be important given the low maximum inspiratory pressure commonly seen in cancer patients. These low values imply respiratory-muscle weakness. The narrow therapeutic window of the methylxanthines and adverse effects may limit their clinical utility. Further research needs to be done to assess what role, if any, levalbuterol and methylxanthines may have for cancer dyspnoea.

Terminal care

As patients approach the last hours or days of life, there may be changes in breathing patterns that relates different from dyspnoea. Rapid shallow breathing, periods of apnoea, and a Cheyne-Stokes respiratory pattern are common end-of-life breathing patterns.\(^7\) A few last reflex breaths may signal death. Family carers should be educated that the comatose patient does not experience these breathing patterns as dyspnoea. Rapid shallow breathing, periods of apnoea, and secretions accumulate. Air passing through these accumulated secretions can create gurgling or crackling sounds colloquially termed the death rattle. Family carers may interpret this pattern as dyspnoea. Anticholinergic medications can be used effectively to dry these secretions;\(^4,8\) panel 4 gives typical medications and doses. Repositioning the patient may also be effective in controlling the sounds. Suctioning is generally ineffective and contraindicated because the site of secretions is inaccessible to the suction catheter in most cases. In addition, the process of suctioning can unnecessarily stimulate an otherwise peaceful patient. Nevertheless, since the anticholinergic agents work best to prevent secretions, gentle suctioning may at times be indicated if other measures have failed.

Refractory dyspnoea

There may be a few patients for whom the symptomatic approaches outlined in this review do not relieve dyspnoea. In these rare cases, sedation can be given ethically for the patient to be relieved of the awareness of the symptom.\(^9\) After informed consent has been obtained, medications such as benzodiazepines, neuroleptics, barbiturates, or propofol may be titrated to induce sedation. Opioids alone are unreliable sedatives. Doses should be titrated to provide the desired degree of sedation. If the intent is sedation, unintended secondary consequences of hastened death are ethical under the doctrine of double effect. This ethical principal is widely accepted among Western cultures.

Conclusions

Dyspnoea is a significant clinical problem for cancer patients. Effective clinical management strategies will relieve the symptom to the satisfaction of the majority of patients. Opioids are the first-line therapy for control of dyspnoea. Oxygen and benzodiazepines may be useful adjuncts. Symptomatic management of dyspnoea can be pursued concurrently with treatment directed at removing underlying causes. For refractory cases, sedation may be appropriate and ethical under the principle of double effect.

### Panel 4. Anticholinergic therapy

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose and Route</th>
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<tbody>
<tr>
<td>Scopolamine</td>
<td>0.2–0.4 mg subcutaneously every 4 h, or one to three times daily</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>0.2 mg subcutaneously every 4–6 h, or 0.4–1.2 mg/day</td>
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References


