

# Management of Dyspnea

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**D**yspnea can be defined as an uncomfortable sensation or awareness of breathing. Patients may describe the feeling as shortness of breath, inability to get enough air, or suffocation. Some are only able to report that their activities are limited by heavy or hard breathing. As in the case presented on the following page, patients may be reluctant to report symptoms unless they are specifically elicited.

The prevalence of dyspnea in cancer patients has been reported to be between 21% and 90%, depending upon the stage of cancer and selection criteria of patients [1–3]. It is particularly common in patients who have primary lung cancer or metastatic involvement of the lung. However, for reasons that are not entirely clear, it is also a common symptom for patients with no direct lung involvement. The National Hospice Study found that 24% of patients had dyspnea with no known cardiopulmonary pathology [3]. In addition, patients who have significant underlying cardiopulmonary problems, such as chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF), also develop cancer.

## Pathophysiology

The pathophysiology of dyspnea is incompletely understood and multifactorial. Most of the well-controlled data are from studies of healthy volunteers with experimentally induced dyspnea or patients with COPD. However, in a prospective

Published data for this review were identified by a search of the MEDLINE database using the search term "dyspnea." Subsets of the original search were also identified by using the additional keywords "pathophysiology" and "therapy," as well as publication type "clinical trial." Additional papers were identified from the personal collections of the authors and from the bibliographies of papers identified by the search strategy described above. Only English-language references published after 1966 were used.

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**Abstract** Patients with cancer frequently report dyspnea, the uncomfortable awareness of breathing. Lung involvement with cancer does not predict its occurrence. Patients describe it as one of the most frightening and distressing symptoms, and patient self-report is the only reliable measure. Measurements of respiratory rate, oxygen saturation, and arterial blood gases do not measure dyspnea. Opioids in modest doses have been demonstrated to give effective relief of dyspnea, whether or not identifiable reversible causes exist. Medical management of dyspnea can be directed at the underlying cause when the potential benefits outweigh the burdens of such treatment. In rare cases where symptomatic treatment is unable to control dyspnea to the patient's satisfaction, sedation is an effective, ethical option.

analysis of 100 patients with dyspnea and advanced cancer, Dudgeon and Lertzman attempted to better identify the causes [4]. They found that 49% had lung cancer; 65% had lung or pleural involvement; 40% were hypoxemic, with an  $O_2$  saturation < 90%; 12% had a  $Pa_{CO_2} \geq \sim 6.0$  kPa (45 mm Hg); 52% had a component of bronchospasm; 29% had evidence of cardiac ischemia, CHF, or atrial fibrillation; and 20% were anemic, with a hemoglobin concentration less than 10 gm%. Pulmonary function tests revealed that 5% had an obstructive pattern, 41% had a restrictive pattern, and 47% had a mixed obstructive/restrictive pattern. The median maximum inspiratory pressure (MIP) was  $-16$  cm  $H_2O$  (normal  $-50$  cm  $H_2O$ ), indicating that respiratory muscle weakness was significant. None had received chemotherapy that causes pulmonary disease, but 40% had radiation therapy that included at least a portion of the lungs. The average number of potential causes of dyspnea per patient was five. Although this study was small, it implies that dyspnea is frequently multifactorial in patients with cancer.

## The Anatomy of Breathing

Respiratory activity is complex [5, 6]. The respiratory center in the medulla and pons coordinates the activity of the diaphragm, the intercostal muscles, and accessory muscles of

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### Case Report

A 57-year-old man with advanced pancreatic cancer was seen in the office for interval evaluation during treatment with gemcitabine (Gemzar). A celiac plexus block had previously provided complete pain relief. Dyspnea was elicited during the interval history. The patient described it as constant, 6/10 in intensity on a visual analog scale, and bothersome. The symptom had been present for 6 weeks but it was not mentioned before. He had lost 40 pounds in 2 months, but had no further weight loss. He was worried that his breathing difficulty meant that he will die soon. Staging evaluation 4 weeks earlier showed stable disease. He was not anemic. Pulse oximetry showed 93% saturation on room air. Morphine 5 mg provided 50% relief. Sustained-release morphine 15 mg every 12 hours and immediate-release morphine 5 mg every hour, as needed, was prescribed. Gemcitabine was administered on schedule.

respiration. It receives sensory information from central and peripheral chemoreceptors in blood vessels; peripheral mechanoreceptors from muscles, tendons, and joints; and pulmonary vagal afferents. These 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 fibers that respond to pulmonary interstitial and capillary pressure. These afferents may also send information directly to the cerebral cortex. It is believed the cerebral cortex integrates this sensory input with other cognitive and emotional factors, as well as with motor information from the respiratory center.

Normally, there is no awareness of breathing. However, if any of these inputs are perturbed, an uncomfortable awareness of breathing may occur.

Cortical areas involved in the perception and modulation of dyspnea have been identified by applying functional brain imaging using positron emission tomography (PET) [7, 8]. These studies implicate areas such as the anterior insula and the posterior cingulate gyrus as locations of particular activity in respiration.

For the clinician, these complex and diffuse data regarding pathophysiology can be conceptually summarized in three components:

1. *Work of Breathing.* The increased effort required for breathing against increased resistance (eg, COPD) or breathing with weakened muscles

(eg, neuromuscular disease or cachexia) is perceived as dyspnea. Most studies point to increased respiratory work as an important component.

2. *Chemical.* Medullary chemoreceptors predominantly sense hypercapnia. Carotid and aortic body chemoreceptors predominantly sense hypoxemia. Signals from these chemoreceptors can produce dyspnea independent of increased respiratory effort [9, 10].

Hypoxemia appears to play a *less* important role than is commonly believed. This conclusion is supported by the observations that it takes moderately severe levels of hypoxemia to trigger the peripheral chemoreceptors [11]. In addition, the compensatory increase in ventilation triggered by hypoxemia drives down the CO<sub>2</sub> level, which then partially negates the effect of the hypoxemia. Finally, many studies have documented that most patients with cancer and dyspnea are not hypoxemic.

3. *Neuromechanical Dissociation.* When there is a mismatch between brain set points and sensory feedback from the periphery, dyspnea occurs [12]. For example, when researchers limit the inspiratory flow rate at which a subject is allowed to breathe, dyspnea results despite no change in respiratory work or chemical status [13].

### Diagnosis

Similar to pain, the only reliable indicator of dyspnea in clinical practice is patient self-report. There is no other reliable, objective measure of dyspnea. Respiratory rate, oxygen saturation, and arterial blood gas determinations neither correlate with nor measure dyspnea. For example, patients may be hypoxemic, but not dyspneic, or dyspneic, but not hypoxemic.

In the clinical research setting, dyspnea may be measured in a number of ways. Functional assessment tools such as the shuttle walking test [14] and the reading aloud of numbers [15] have been validated. When functional assessment is difficult or when perceptions are targeted, scales such as the visual analog [16] and Borg [17] scales have been validated. These measures are simple and reproducible. Visual analog scales typically have a 100-mm line with verbal descriptors such as “no breathlessness” and “worst possible breathlessness” anchoring the ends. A patient makes a mark on this line corresponding to how much dyspnea is experienced. The modified Borg scale is a 10-point scale with descriptors anchoring the ends of the

scale and specific numbers within the scale. Absolute answers promote improved interindividual comparison.

In clinical practice, such measurement scales are impractical and burdensome. In addition, many patients are unable to make the abstract connection between a scale and their sensation of dyspnea.

### Clinical Approach

Approach the assessment of a patient who is dyspneic in a thorough, stepwise fashion. Begin with the history. Include an assessment of the patient's psychosocial and spiritual domains. Questions like:

- "What does this symptom mean?"
- "What effect does this have on your daily life?"
- "What sense have you made of this symptom?"

will frequently elicit informative perspectives. Stressors in these areas may be affecting or exacerbating the symptom. They are important to identify because reassurance, active listening, and referral for interdisciplinary support will be therapeutic. Similarly, drug therapy will not alleviate psychosocial or spiritual concerns. Past medical history, smoking history, occupational history, and prior radiation or chemotherapy may provide additional diagnostic clues.

A physical examination in conjunction with simple studies such as pulse oximetry, a complete blood count, and a chest x-ray are most often sufficient to clarify an understanding of the pertinent pathophysiology. They will not, however, clarify whether the patient has dyspnea—they will only help the clinician conceptualize likely causes.

In our experience, pulse oximetry is the most frequently misused test in this regard. Continuous pulse oximetry is frequently applied to the patient who is dyspneic without regard to what changes in clinical management will rest on the results. The patient and family focus on the monitor. Decreases in pulse oximeter values yield anxiety and worsen dyspnea. Therefore, if indicated, measure the percent saturation, then remove the monitor.

The possible benefits of investigation must be weighed against the burdens *before* they are ordered. It is not infrequent that studies such as arterial blood gas determinations, pulmonary function tests, CAT scans, echocardiograms, or ventilation-perfusion scans may only satisfy the clinician's curiosity rather than materially help the

**Table 1**  
Causes of Dyspnea

<b>Directly related to cancer</b>
Primary/metastatic parenchymal lung involvement
Airway obstruction (intrinsic or extrinsic tumor)
Carcinomatous lymphangitis
Pleural tumor
Malignant pleural effusion
Pericardial effusion
Superior vena cava syndrome
Tumor microemboli
Phrenic nerve paralysis
Atelectasis
Tracheal esophageal fistula
Chest-wall invasion (carcinoma en cuirasse)
Pathologic chest-wall fractures
<b>Indirectly related to cancer</b>
Pneumonia
Cachexia
Anemia
Electrolyte abnormalities
Pulmonary embolus
Paraneoplastic syndromes
Ascites
<b>Related to cancer therapy</b>
Surgery (postlobectomy/pneumonectomy)
Radiation pneumonitis
Chemotherapy-induced pulmonary fibrosis
Chemotherapy-induced cardiomyopathy
<b>Unrelated to cancer</b>
Chronic obstructive pulmonary disease
Asthma
Congestive heart failure
Cardiac ischemia
Arrhythmias
Pulmonary vascular disease
Obesity
Neuromuscular disorders
Aspiration
Anxiety
Pneumothorax
Interstitial lung disease
Psychosocial/spiritual pain

patient. Possible specific etiologies of dyspnea are listed in Table 1.

### Symptomatic Management

The therapeutic goal of symptomatic management of dyspnea is to relieve the patient's sense of the effort of breathing. This can be achieved by pursuing one or more strategies, including both phar-

macological and nonpharmacological interventions. These strategies need not be limited to those for whom efforts to relieve the underlying causes are thought to be futile or excessively burdensome.

**OPIOIDS**

Opioids have been shown to be the most effective pharmacological agents for symptomatic control of dyspnea. Studies have demonstrated that acute therapy with opioids decreases exercise-induced dyspnea and increases exercise tolerance in COPD patients [18, 19]. Bruera et al [20] were the first to study the use of opioids for controlling dyspnea in cancer patients. They demonstrated in a placebo-controlled crossover study that opioids relieved dyspnea without evidence of respiratory depression. There was no change in respiratory rate or oxygen saturation. Mazzocato et al [21] showed that as little as 5 mg of morphine sulfate delivered subcutaneously was effective in controlling dyspnea in opioid-naïve patients. The duration of the effect on dyspnea was consistent with the serum half-life of morphine and equivalent to that observed for pain relief—about 4 hours. For patients on baseline opioids, Allard et al [22] showed that a 25% increase in the baseline dose provided breakthrough relief of dyspnea for up to 4 hours.

Once an effective dose has been determined, a typical opioid regimen to maintain control of chronic dyspnea would include both a sustained-release

opioid for baseline control and an immediate-release opioid for breakthrough dyspnea.

The mechanism by which opioids relieve dyspnea is not well understood. The fact that systemic administration of naloxone, an opioid antagonist, increases dyspnea supports the role that endogenous opioids play in controlling dyspnea [23]. Opioid receptors are located throughout the peripheral and central nervous system. As previously noted, functional brain imaging with PET scans have identified cortical areas putatively involved with the perception and modulation of dyspnea [7, 8]. These areas seem to co-localize with areas previously linked to the perception of pain. Thus, although circumstantial, it is possible that opioids alter the perception of dyspnea in a manner analogous to their alteration of the perception of pain.

Opioid receptors have also been identified throughout the tracheobronchial tree, with the highest concentrations in the alveolar walls [24]. Nebulized opioids, at levels thought to have minimal systemic absorption, have been observed to relieve dyspnea in uncontrolled trials and anecdotally. The clinical role for the opioid receptors in the lung was thus imputed. However, several clinical studies of nebulized opioids have failed to demonstrate this effect [25]; 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 dyspnea when prescribed according to the guidelines outlined in Table 2. Guidelines are also provided in the table for patients with compromised pulmonary status, such as COPD.

Light et al [19] studied 13 COPD patients with an average FEV<sub>1</sub> (forced expiratory volume in one second) of 0.99 liters, Pa<sub>CO2</sub> < 6.1 kPa (46 mm Hg), and Pa<sub>O2</sub> > 7.3 kPa (55 mm Hg). They were given an oral morphine dose of 0.8 mg/kg prior to exercise. A 70-kg opioid-naïve patient would have received 56 mg of oral morphine in this study. This dose is many times larger than a typically effective starting dose of 2.5–5 mg of morphine for a COPD patient who has not been taking any opioid medications. Although there was an increase in Pa<sub>CO2</sub> and decrease in Pa<sub>O2</sub>, respirations were not suppressed in a life-threatening way, and, in fact, dyspnea and exercise tolerance improved.

Poole et al [26] failed to demonstrate any benefit of sustained-release morphine for 16 COPD patients using the Chronic Respiratory Disease Questionnaire (CRQ). In this study, patients had

**Table 2**  
Opioid Therapy for Dyspnea

<p><b>Opioid-naïve patients</b></p> <p><i>Mild dyspnea</i></p> <ul style="list-style-type: none"> <li>• Hydrocodone 5 mg PO q4h or codeine 30 mg PO q4h</li> <li>• For breakthrough symptom management, give an equivalent dose q1–2h, as needed</li> </ul> <p><i>Severe dyspnea</i></p> <ul style="list-style-type: none"> <li>• Morphine sulfate 5 mg PO q4h, oxycodone 5 mg PO q4h, or hydromorphone 1 mg PO q4h</li> <li>• For breakthrough symptom management, give an equivalent dose q1–2h, as needed</li> <li>• Titrate up in increments of 50%–100% every 24 hours, as needed.</li> </ul> <p><i>Note: 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 hours, as needed.</i></p> <p><b>Opioid-tolerant patients</b></p> <p>Increase baseline opioid dose by 25%–50% and titrate as above.</p>
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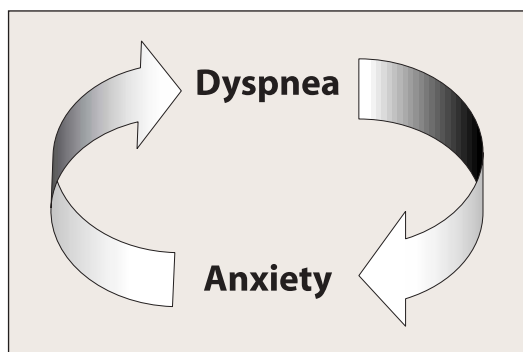
an average FEV<sub>1</sub> of 0.6 liters, Pa<sub>O<sub>2</sub></sub> > 8.5 kPa (65 mm Hg), and Pa<sub>CO<sub>2</sub></sub> < 5.5 kPa (40 mm Hg). Patients reported opioid-related side effects (predominantly nausea, constipation, and drowsiness) that limited their average morphine dose to 25 mg/day. No clinically or statistically significant decrease in oxygen saturation associated with morphine administration was observed. The researchers observed no difference in the CRQ total score, but on a subscore of mastery, patients on morphine fared worse. Although patients treated with morphine tended to show improvement on a subscale for dyspnea, it was not significant. Nevertheless, 9 of 14 patients who completed the study chose to continue morphine after the completion of the study, and 1 of the 14 exhibited a significant improvement in exercise tolerance and decrease in dyspnea. This study demonstrated that chronic opioid dosing was safe in terms of respiratory depression even in a severe COPD population with an average FEV<sub>1</sub> of 0.6 liters.

The adverse effects of opioids are as important in dyspnea as they are in pain management. Fortunately, they can be managed. Untreated opioid side effects, such as constipation, lethargy, and nausea, affect quality of life [26, 27]. Except for constipation, patients become pharmacologically tolerant to all of the adverse effects of opioids, such as sedation and nausea, within 1–2 weeks [28]. If needed, stimulants (for example, methylphenidate) and antidopaminergic anti-emetics (such as prochlorperazine [Compazine]) can be prescribed temporarily to control these adverse effects. For constipation, all patients on opioids should be treated with an effective bowel regimen to *prevent* constipation. This typically consists of both a stimulant laxative (eg, senna) and a stool softener (eg, docusate sodium).

## ANXIOLYTICS

Patients frequently report anxiety in association with dyspnea. Dyspnea can lead to anxiety, but not always, and anxiety can exacerbate dyspnea, but not always (Fig. 1). Many patients may not be able to distinguish between anxiety and dyspnea—they are experienced simultaneously.

Therapeutically, it is useful to distinguish anxiety from dyspnea. Opioids alone may break the cycle by relieving dyspnea, which can help distinguish dyspnea from anxiety, since opioids do not have a sustained anxiolytic effect. While the opioids may initially have anxiolytic properties, this



**Figure 1** Interrelationship Between Dyspnea and Anxiety

can be viewed as a side effect. As with other side effects of opioids (except constipation), patients typically become tolerant to the anxiolytic effect. Therefore, anxiolytic properties alone do not explain the opioids' effect on dyspnea.

Anxiolytics (such as benzodiazepines) are frequently prescribed for patients with dyspnea. However, when tested as the *only* treatment for dyspnea, they are not effective. In a placebo-controlled single-blind study of four COPD patients, Mitchell-Heggs et al [29] demonstrated that moderate doses of diazepam improved dyspnea. However, subsequent double-blind studies on healthy subjects or COPD patients with diazepam or alprazolam failed to show any benefit over placebo [30–32]. Dudgeon and Lertzman [4] found anxiety to be correlated with dyspnea; but in their multivariate model, it was sufficient to explain only 10% of the variance of dyspnea.

These data support the assertion that benzodiazepines alone should not be used as first-line therapy for dyspnea. Relief of dyspnea by other means, such as opioids, may be sufficient. However, treatment of anxiety does have a role in a subset of patients for whom anxiety is a prominent component of their distress. For these patients, benzodiazepines may be safely prescribed at appropriate doses (Table 3). They may be prescribed in conjunction with opioids without fear of respiratory depression when these guidelines are followed. Additionally, chlorpromazine [33], a major tranquilizer, and buspirone (BuSpar) [34], a non-benzodiazepine anxiolytic, have been reported to decrease dyspnea.

## OXYGEN

Supplemental oxygen can reverse hypoxemia. If lack of oxygen is the cause of dyspnea, oxygen may be the only required therapy. However, its perceived benefit in

**Table 3**  
Anxiolytic Therapy for Dyspnea

<b>Lorazepam</b>
0.5–1 mg PO q1h until dyspnea is settled, then dose routinely q4–6h to keep settled
<b>Diazepam</b>
5–10 mg PO q1h until dyspnea is settled, then dose routinely q6–8h
<b>Clonazepam</b>
0.25–2 mg PO q12h
<b>Midazolam</b>
0.5 mg IV every 15 min until dyspnea is settled, then give by continuous SC or IV infusion

patients with cancer who are dyspneic far exceeds the number who are demonstrated to be hypoxemic.

There have only been a few small studies assessing oxygen therapy for hypoxemia in cancer patients. Bruera et al [35] observed that oxygen improved dyspnea in cancer patients in a randomized, double-blind crossover study. However, another controlled study showed no advantage of oxygen over compressed air [36]. As described earlier, hypoxemia is a relatively weak stimulus for dyspnea. Many patients are dyspneic but not hypoxemic;  $Pa_{O_2}$  has not been found to correlate with subjective reports of dyspnea. Some patients have noted improvement in dyspnea with oxygen despite unrelieved hypoxemia. The relief of dyspnea observed with oxygen is likely a placebo effect if:

First, the patient identifies that he or she cannot get enough “air.” Supplemental oxygen appears

## PEER VIEWPOINT

*Commentary by Wendy French, DO, Patrick Coyne, MSN, RN, and Thomas J. Smith, MD*

**M**anagement of Dyspnea” by Thomas and von Gunten is a comprehensive review of the literature on the prevalence, pathophysiology, possible mechanisms, causes, and standard treatment of cancer-related dyspnea. Dyspnea is an extremely common symptom in cancer patients, experienced by 50% to 70% of terminally ill patients in the final weeks of life [1]. We, as healthcare providers, should be quick to assess its presence in our patients and provide adequate symptom relief. Unfortunately, such relief is achieved less often for dyspnea than it is for pain or nausea [2], and families often report it as an overlooked, but distressing, symptom.

Often, there are no identifiable causes for dyspnea. As with pain, we must believe what the patient tells us about the presence and severity of dyspnea. Several studies have failed to correlate physical or demographic data to the presence or degree of dyspnea [3]. However, as stated in the accompanying review, there is substantial evidence that dyspnea is treatable.

Opioids were first reported as effective treatment for exertion-induced breathlessness in the 1980s [4]. Since that time, they have been administered in a variety of ways, including orally, subcutaneously, by IV, and via nebulizer. Anecdotes, case reports, and controlled trials of can-

cer patients all confirm the benefit of opioids for relief of dyspnea. A Cochrane review in 2001 found “statistically strong” evidence that opioids were effective in treating cancer-related dyspnea [5].

### CONTROVERSY

An area of controversy in the treatment of dyspnea is the use of nebulized opioids. In a minireview, Zebraski et al [6] describe the earlier works of Cabot, who reported the presence of opioid receptors in the periphery of the lungs of rats. “Nonconventional” opioid-binding sites were discovered, with the highest number of binding sites being in the alveolar wall and in the smooth muscle of the trachea and bronchus. These data have been the basis for subsequent human studies using nebulized opioids.

The results of these studies have been inconsistent. Many uncontrolled, nonrandomized studies, case reports, and chart reviews describe improvement in dyspnea, contributing to a growing body of anecdotal evidence supporting the use of nebulized opioids [7–9]. However, several controlled studies using nebulized opioids have provided inconclusive or negative results. Testing was performed on healthy volunteers and patients with pulmonary and cardiac diseases, a population very different from those with advanced cancer. Another criticism of these studies is the lack of dose titration of the nebulized opioid.

to remediate that deficiency.

Second, supplemental oxygen is a potent symbol of medical care. The distressed patient feels that the healthcare team is “doing something.”

Finally, the need to “do something” is strong among those caring for a dyspneic patient. “Putting on oxygen” is something most clinicians learn in the first days of clinical training.

There may be other explanations for the perceived effectiveness of supplemental oxygen. It has been observed that cool air blowing on the face (eg, sitting in a breeze or in front of a fan) reduces dyspnea. Several studies support the hypothesis that stimulation of the trigeminal nerve (V<sub>2</sub> branch) has central inhibitory effects on dyspnea [37–39]. Part of oxygen’s effect may therefore be due to this sensory stimulation, rather than cor-

rection of hypoxemia or a pure placebo effect. Thus, one can consider cool, moving air for all dyspneic patients.

There are burdens associated with the provision of supplemental oxygen therapy. It is costly and cumbersome. For many patients, it unnecessarily restricts their mobility and alters their self-image. In addition, clinicians may not explore the other symptomatic therapies that can render the patient comfortable and less dependent on the requisite equipment needed for oxygen therapy.

### Cognitive/Behavioral Interventions

Dyspnea has cognitive and emotional components in addition to the pathophysiological components. Bredin et al [40] conducted a multicenter, randomized, controlled study that evaluated the

We do know that systemic absorption is low with nebulized morphine [10], and systemic side effects appear to be minimal, so at least it is rarely toxic. A phase II study by Coyne et al [11] reported improvement in dyspnea and oxygen saturation with nebulized fentanyl, now being tested in a randomized clinical trial. One report of dyspnea relief in three patients by nebulized furosemide needs to be confirmed [12].

Improvement in the treatment of cancer-related dyspnea is needed. Hopefully, advances in treatment will come from future randomized, controlled trials to determine optimal doses, schedules, and routes of opioid administration.

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effect of a nurse-run dyspnea clinic. The concept is similar to pulmonary rehabilitation clinics for COPD. The intervention consisted of teaching breathing control, activity pacing, relaxation techniques, and psychosocial support. Relative to controls, the patients who underwent the intervention showed improvement in dyspnea scores, performance status, and emotional states. Thus, nonpharmacological therapies have a role in the control of dyspnea.

The clinician managing a patient with dyspnea is an important therapeutic instrument. A calm, confident demeanor is reassuring to the patient and family and helps to diminish the anxiety component. By contrast, the clinician who responds to the frightened, anxious, dyspneic patient with a similar response is likely to have the opposite therapeutic effect.

### Management of Underlying Causes

The patient's functional status and prognosis are important factors to consider before developing a plan for diagnostic workup and choice of therapeutic interventions. Ascertain the patient's goals and the reversibility of potential underlying causes *before* developing the plan. The treatment plan may be directed at reversible causes at the same time that measures to control symptoms are instituted.

Dyspnea directly related to the cancer can potentially be treated with resection, chemotherapy, or radiation therapy. Obstruction can be treated locally with laser therapy, cryotherapy, or stenting. Malignant pleural effusions can be drained by thoracentesis, and if they prove recurrent, pleurodesis may be attempted. Fluid drainage may improve the mechanical advantage of the respiratory muscles to relieve dyspnea [41].

Red blood cell transfusion remains controversial. Studies have shown qualitative improvement in symptoms, but there has been no clear correlation with pre-transfusion hemoglobin levels [42]. Therefore, transfusion therapy needs to be individualized. For anemia-related dyspnea, erythropoietin (Epogen, Procrit) is slowly effective and avoids the risks of transfusion but requires time (months) to be effective 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 (Atrovent) treat reversible bronchospasm. Recently, the stereoisomers of the selective  $\beta_2$ -agonist albuterol have been isolated and clinically tested. The S-isomer appears to be pro-inflammatory, and so a purified R-isomer known as levalbuterol (Xopenex) has been introduced clinically. Similarly, studies in asthma indicate the R-isomer may induce bronchodilation at a lower concentration than racemic albuterol and, consequently, has less  $\beta$ -adrenergic side effects [43]. 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 reduced maximal inspiratory pressure (MIP) commonly seen in cancer patients. These reduced MIP values imply respiratory muscle weakness. The narrow therapeutic window of the methylxanthines and their adverse effects may limit their clinical utility. Further research needs to be done to assess what role, if any, levalbuterol and the methylxanthines may have for cancer-associated dyspnea.

Avoid the temptation to treat the dyspneic patient with bronchodilators *as if* the patient had a bronchospastic component. While a therapeutic trial may be warranted, stop the therapy if there is no response. A prominent adverse effect of inhaled bronchodilators is anxiety. The treatment may paradoxically worsen dyspnea.

### Terminal Care

As patients approach the last hours or days of life, there may be changes in breathing patterns that the family or loved ones interpret as dyspnea. Rapid shallow breathing, periods of apnea, and a Cheyne-Stokes respiratory pattern are common end-of-life breathing patterns [44]. A few last reflex breaths may signal death. It is important to educate family caregivers that the comatose patient does not experience these breathing patterns as dyspnea. In some cases, to alleviate the suffering of family caregivers, low-dose opioids or benzodiazepines may be appropriate to manage any perception of breathlessness in a comatose patient by lowering the respiratory rate to within a normal range. There is no known adverse effect on the comatose patient, and this management can significantly

**Table 4****Anticholinergic Therapy for Dyspnea**

<b>Scopolamine</b>
0.2–0.4 mg SC q4h or 1.5 mg transdermal patch 1–3 q72h or 0.1–1 mg/h via continuous IV or SC infusion
<b>Glycopyrrolate</b>
0.2 mg SC q4–6h or 0.4–1.2 mg/d via continuous IV or SC infusion

soften the experience of the dying process for the family.

As death approaches, the gag reflex and reflexive clearing of the oropharynx decline and secretions accumulate. Air passing through these accumulated secretions can create gurgling or crackling sounds colloquially termed the “death rattle.” Family members may interpret this pattern as dyspnea. Anticholinergic medications can be effectively used to dry these secretions [44]. Table 4 provides a list of typical anticholinergic medications and doses.

Repositioning the patient may also be effective in controlling the sounds. Suctioning is usually ineffective and relatively contraindicated because the site of secretions is often inaccessible to the suction catheter. In addition, the process of suctioning can unnecessarily stimulate an otherwise peaceful patient. However, suction of visible pooled secretions in the posterior oral cavity may be effective.

**Refractory Dyspnea**

There may be a few patients for whom the symptomatic approaches outlined in this review do not provide sufficient relief. In these rare cases, it is ethical to provide sedation in order for the patient to be relieved of the awareness of the symptom [45]. Sedating medications, such as benzodiazepines, neuroleptics, barbiturates, or propofol (Diprivan), may be titrated to 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. Sedation for refractory symptoms is legal in all 50 of the United States. Dose escalation for the intent of hastening death is illegal in all 50 states.

**Summary**

Dyspnea 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 symptomatic control of dyspnea. Oxygen and benzodiazepines may be useful adjuncts. Symptomatic management of dyspnea 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.

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## Dyspnea

## PEER VIEW POINT

*Commentary by Rita Wickham, PhD, RN, AOCN, CHPN, and Monica Malec, MD*

In this issue, Thomas and von Gunten have provided a cogent review of the research-based literature, as well as helpful clinical comments, regarding dyspnea in cancer patients. As is evident to the reader, most research has focused on measurement or assessment, with little data to support evidence-based clinical interventions. This is understandable, given the potential clinical and ethical dilemmas encountered with implementing studies that would include individuals with life-limiting disease.

Defining dyspnea is limited by our language and experience—most people have never experienced severe or lasting shortness of breath and can only imagine what it must be like. Dyspnea, from the Greek words for hard and breathing,

may be acute and reversible or chronic and progressive. Patients may suffer alone with progressive shortness of breath for weeks to months because healthcare professionals do not address it, and patients often report that physicians and nurses do not seem to understand their symptom experience or provide concrete and useful solutions to deal with shortness of breath [1, 2].

For example, 77% of hospice patients in one study reported feeling short of breath, but nurses documented dyspnea in only 39% of these patients' charts [3]. Given that estimates of the incidence of dyspnea in cancer patients range so widely, many dyspneic patients *must* be unrecognized and untreated. While dyspnea is most common in patients with lung cancer, it also occurs quite often in those with breast, colorectal or prostate cancers and can occur with virtually any solid or hematological malignancy [4, 5].

We agree that logical, stepwise assessment is the key to management. Even before eliciting the history, initial patient observations may provide valuable information about respiratory status:

- Is the patient receiving supplemental oxygen, and by what means (nasal cannula, rebreathable face mask)?
- Does the patient seem to be “working” to breathe (use of accessory muscles, staccato speech, rapid respiratory rate)?
- Is the patient sitting straight up or leaning forward, and does he or she look anxious?

### GOOD QUESTIONS TO ASK

Evaluating a patient’s self-report of breathing difficulty may not be straightforward because patients’ language for dyspnea most likely differs from ours. Patients have described dyspnea as like not being able to get enough air; feeling out of breath or winded; or having sensations of suffocation, chest tightness, or drowning. Beginning a discussion with a comment such as, “I notice you look like your breathing is difficult/you don’t seem to be getting enough air. Can you tell me about this?” may provide information about the severity, quality, and effects of dyspnea.

Assessment should include aggravators and alleviators of dyspnea. Patients with progressive dyspnea discover that triggers increase over time. Triggers can include physical activities, mechanical activities (crying, laughing), environmental factors (heat, cold, pollen, humidity, smoke), and emotional factors (anger, anxiety). Asking the patient how dyspnea affects their home life, work, and social activities is important, too.

Physical limitations can be estimated by responses to questions about how far patients can walk (those with progressive dyspnea often “push” themselves) or how many steps they can climb before having to stop or rest, as well as what types of activities they have already stopped because of dyspnea. Patients usually discover things that alleviate their dyspnea: they rest more; they position themselves in an upright position to expand their chest cavity; they take medications that seem to help. Thus, telling patients to “rest more,” “avoid activities that increase shortness of breath,” or to “conserve energy” are *not* viewed as helpful suggestions.

### PALLIATIVE AND DEFINITIVE MANAGEMENT

Palliative care, which focuses on managing

symptoms and enhancing quality of life, is not incongruent with therapies to alleviate underlying disease. When the goal of care is clearly comfort, we may need to remind the patient, family members, and even physician and nurse colleagues that “objective measures” are much less important than how the patient’s breathing feels.

Medications form the cornerstone of management. However, anxiolytics, particularly benzodiazepines, are probably much overused. This is because many physicians and nurses view these drugs as being safer than opioids, and dyspneic patients do look anxious and may report pain or anxiety as not being able to breathe. However, anxiolytics can decrease the respiratory response to hypoxia and cause excessive sedation (which is frequently misinterpreted as an adverse effect of concomitantly administered opioids). When anxiety is clearly a separate component and is compounding patient distress, a relatively non-sedating drug such as clonazepam (Klonopin), should be selected.

Bronchodilators, including nebulized or inhaled  $\beta_2$ -adrenergic agonists and oral methylxanthines, should be used only if the underlying illness (chronic pulmonary obstructive disease, some cases of lung cancer) dictates potential benefit. Beneficial and adverse effects must be carefully balanced. Does this drug make the patient feel better, or are nebulizers used at night making the patient feel tired? More importantly, does the patient have dose-limiting adverse effects (palpitations, tachycardia, arrhythmia, tremor, headache, nausea, increased cough, or increased anxiety)?

Conversely, corticosteroids and opioids are very often beneficial. In addition to decreasing shortness of breath, corticosteroids offer additional benefit for patients who may also be experiencing pain, nausea, and fatigue. Opioids, which have been used to decrease the sensation of dyspnea for more than a hundred years, are superior to other agents. They may act at peripheral and central receptors to alter perceptions of breathlessness, decrease respiratory drive, and decrease ventilatory responses to hypoxia and hypercapnia [6].

While lower doses than are used for pain usually alleviate dyspnea, some patients require quite large opioid doses or rapid escalation of IV opioids for severe and rapidly worsening dyspnea. As with pain, appropriate dosing means titration to optimal effect—more comfortable

## PEER VIEWPOINT

breathing without uncontrollable adverse effects. Patients may become somewhat sedated with initial doses, but this is not usually dose-limiting or problematic if they are easily arousable. If a patient is somnolent and very difficult to arouse, a dose can be held or decreased by 50% until the patient is more alert. Naloxone (Narcan) should be avoided.

Delirium is a more common, dose-limiting effect of morphine and is manifested as confusion or visual hallucinations. Delirium may even occur at the lower doses of morphine usually prescribed to treat dyspnea and will increase the patient's and family's distress. Tolerance to delirium does not develop, so if a patient has already experienced these symptoms with the use of morphine for pain control, another opioid might be a better choice to manage the dyspnea. A common misconception is that morphine, but not other opioids, can be used for treating dyspnea.

### COMMON MISCONCEPTIONS

Many nurses and physicians remain unclear about the purpose of opioids for dyspnea and think that use of an opioid will hasten a patient's death. There is no evidence that opioids shorten life or that higher doses correlate with shorter survival [7]. Current thinking is that alleviating dyspnea decreases the exhaustion that can occur with increased work of breathing, which may actually help the patient live longer (and certainly better) [8]. In addition, house-staff physicians and nurses may not understand why morphine or another opioid is being ordered for a patient who does not have pain, or how it should be administered for shortness of breath. Thus, orders should be clear and specific, such as "oxycodone 5 mg po q2h for dyspnea," or for pain, as the case may be.

In addition, the house-staff and nurses involved in a patient's care

should have the opportunity to have questions regarding treatment asked and answered, as their comfort with using opioids for dyspnea *must* be attained, but cannot be demanded.

Nonpharmacological, complementary measures are generally low cost, relatively easy to learn, and beneficial to some patients. As Bredin and colleagues [9] pointed out, concrete suggestions and teaching patients about useful strategies, such as relaxation techniques, breathing control, and activity-pacing are important to successful self-management. Other non-drug measures that may help include acupressure, acupuncture, behavioral modification, and teaching patients diaphragmatic and pursed-lip breathing [8, 10, 11]. And even simpler measures, such as allowing cool air from a table fan to blow on the patient's face or applying cool compresses to the cheek, often decrease the feeling of breathlessness.

### SOME PRACTICAL CONSIDERATIONS

We agree that aggressive symptom management is particularly important in dying people, not only for the patient's comfort but for the family members as well, for they may never forget the anguish of watching a loved one gasping for breath or dying in pain. It is also important to help family members realize that certain breathing patterns are not distressing to the patient. We also need to remember practical interventions, such as decreasing fluid intake as renal function declines. This is especially important when managing hospitalized patients, because IV hydration is often added reflexively and believed not to carry any burden. Families may associate fluids and feedings with nourishment and comfort. They need to be educated and reassured that stopping these interventions will not increase distress, but, in fact, continuing them may increase pulmonary secretions and respiratory distress. If a scopolamine patch is used to dry accumulated secretions, we apply it in a location without edema and with good circulation, rath-

er than behind the ear, which is used purely for cosmetic reasons and ease of access,

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