Dyspnea

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ABSTRACT

Dyspnea, defined as uncomfortable or labored breathing, is a common and often devastating cause of distress for patients and their caregivers with advanced cancer and other life-threatening illnesses. The mechanism by which dyspnea develops is not fully understood, but it involves integration of the central respiratory complex with the sensory (perceptual) cortex. The gold standard of diagnosis is patient self-report. Careful assessment should be undertaken to identify reversible existing causes. Systemic opioids are the first-line therapy for symptomatic management, along with other general comfort measures (positioning, cool air, calming environment). Medical or surgical management can be directed toward underlying causes. Advanced care planning should include discussions concerning the burdens and benefits of medical/surgical management of underlying causes of dyspnea to more effectively direct goals of care. This article reviews current literature on dyspnea, with a focus on items published since 2000. (Cancer J 2006;12:365–373)

KEY WORDS

Dyspnea is a sensation described as uncomfortable or unpleasant labored breathing.1 It is a subjective experience of perceived breathlessness or difficulty breathing that may not correlate with physical symptoms or biochemical parameters. Dyspnea or breathlessness is experienced by most cancer patients in the last weeks of their life and is by far one of the most common symptoms noted in the last 48 hours of life.2

The prevalence of dyspnea depends on the type of cancer and other underlying conditions. Ranges from 19% to 64% have been reported, with moderate dyspnea being reported in up to 55% of patients with terminal cancer.3 Dyspnea is reported to be as high as 84% for lung cancer and occurs in greater than 50% of individuals with breast, lymphoma, genitourinary, and head and neck cancers.4 A low Karnofsky performance score (40 or less) correlates with increasing frequency of dyspnea, drowsiness, weakness, and confusion.5 Other factors have been reported to correlate with the degree and intensity of the dyspnea experience (Table 1).

Quality of life is affected by the degree or severity of dyspnea.6 Physical and overall functional status, including independence in daily activities (caring for oneself, going out of the house, independent travel), is decreased, leaving these individuals with increased feelings of isolation and hopelessness. Emotional well-being is also affected because the sensation of breathlessness can lead to anxiety, fear, nervousness, or panic.7

The multidimensional nature of dyspnea, including physiologic, psychological, environmental, and social factors, contributes to the difficulties in obtaining adequate symptom control. Thus, dyspnea symp-

### TABLE 1

**Risks Factors and Correlates for Moderate- to-Severe Dyspnea in Patients with Cancer**

| Risk Factor | Description |
|-------------|-------------|
| Smoking     | —past or present |
| Chronic obstructive pulmonary disease | |
| Cardiac disease, especially congestive heart disease | |
| Asthma      | |
| Environmental exposures (asbestos, coal dust, cotton dust, grain dust) | |
| Lung radiation | |
| Lung cancer—primary or metastatic | |
| Anxiety—either as cause or effect of dyspnea | |
| Fatigue/tiredness | |
| Maximal inspiratory pressure < 80% predicted | |
| Vital capacity < 80% predicted | |
| Low Karnofsky performance score | |

Data from Dudgeon et al4 and Bruera et al.3
tom control is less frequently obtained than is control
of other symptoms confronting cancer patients.

**MECHANISMS OF DYSPNEA**

Figure 1 summarizes the need to breathe and the factors that are associated with the perception of breathlessness. The respiratory center, located in the medulla, receives information via afferents from chemoreceptors, baroreceptors, mechanoreceptors, and stretch receptors in the lung and the cerebral cortex. Respiratory motor activities via efferent neurons stimulate the respiratory muscles to expand the chest wall, inflate the lungs and produce ventilation. The entire respiratory control system functions to maintain homeostasis of metabolic parameters within the body (pH, partial pressures of oxygen and carbon dioxide).

Chemoreceptors located in the medulla are sensitive to minute changes in pH. Hypercapnia via central chemoreceptors and hypoxia via peripheral chemoreceptors on the carotid body and aortic body stimulate increased respiratory motor activity and the sensation of dyspnea. However, not all patients with hypoxia feel dyspneic, and as a corollary, not all hypoxic patients are dyspneic. Mechanoreceptors in the lung and chest wall respond to irritants and pulmonary stretch such as would be found in pulmonary edema. An increase in added external ventilatory load mediates the sensation of dyspnea. The conscious awareness (sensory cortex) of the outgoing respiratory motor command to the respiratory muscles is thought to be distinct from the sensations directly related to changes in respiratory muscle length or tension. This corollary discharge from the respiratory centers in the medulla to the sensory cortex serves as a functional pathway for the sensation of dyspnea. The sense of respiratory effort (dyspnea) increases as commands from the central motor respiratory center intensify afferent discharges to the respiratory muscles.¹

Finally, there are several known modulators that can increase or decrease the intensity of dyspnea. Individuals with asthma and chronic obstructive pulmonary disease (COPD) show great variability in the expression of dyspnea, especially when compared with abnormalities in pulmonary function testing. Anxiety appears to be an independent correlate of the intensity of dyspnea in patients with cancer and is also present in individuals with lung disease who have a disproportionate sense of dyspnea compared with findings on pulmonary function testing.²³

The mechanisms of dyspnea, although not fully delineated, are thought to involve (1) an increase in ventilatory requirement via chemoreceptors in the blood and brain, mechanoreceptors in the airways, lung, and chest wall and lung stretch and irritant receptors to maintain metabolic homeostasis; (2) an increase in respiratory effort in order to overcome a load, such as is experienced with COPD, pleural effusion, or restrictive lung diseases; or (3) an increase in the proportion of respiratory muscle required to maintain a workload, as experienced in cancer.

**FIGURE 1** Mechanisms of dyspnea.
cachexia, neuromuscular diseases, or anemia. Symptom management attempts to identify a physiologic cause or causes for dyspnea.1

**ASSESSMENT**

There is no objective test to measure the subjective sensation of dyspnea. Assessment of this symptom is based on the patient's self-report. A full assessment needs to be multidimensional in scope not only to include the patient's description of their symptom but also to search for other underlying causes, with special attention being given to the role that anxiety, depression, summarization, and pain may play in the expression of this symptom.10 The etiology of dyspnea in advanced cancer can be multifactorial and compounded by the influence of psychological, emotional, environmental, and other social factors (Table 2).

In studies that attempted to define the “language of breathlessness” (Table 3), descriptors were identified to guide the clinician toward the underlying etiology of a patient's symptom.11-14 Understanding these descriptors is an important part of the history. Clinicians should ask specific questions regarding the quality, characteristics, onset, and precipitating factors for breathlessness as part of obtaining a medical history.15,16 The goal in the assessment and treatment of dyspnea is to evaluate and treat, if possible, any underlying conditions contributing to dyspnea in patients with cancer.

The cornerstone in the evaluation of dyspnea is a sound history and physical examination (Table 4). The history should focus on the onset (acute vs progressive), exacerbating or relieving factors, association with other symptoms (pain, cough, fever, and anxiety), intensity, and subjective descriptors that the individual uses. A history of smoking, other medical conditions (asthma, COPD, heart disease), occupational exposures, prior radiation therapy, or chemotherapy can help guide further evaluation and treatment modalities. As with any patient, the burdens of an extensive work-up should be balanced with the patient's desires and quality of life.

| **TABLE 2** Common Causes of Dyspnea in Patients with Advanced Cancer |
|------------------------------------------|
| Related directly to the tumor             |
| Pulmonary mass or metastasis             |
| Bronchial or tracheal obstructions        |
| Pleural effusion                         |
| Pericardial effusion                     |
| Carcinomatous lymphangitis                |
| Superior vena caval syndrome             |
| Indirectly related to advanced cancer    |
| Anorexia/cachexia                        |
| Anemia                                   |
| Infection                                |
| Pulmonary embolism                       |
| Deconditioning                           |
| Related to treatment                     |
| Radiation pneumonitis                    |
| Chemotherapy-induced pulmonary fibrosis  |
| Chemotherapy-induces cardiomyopathy      |
| Postpneumonectomy                        |
| Unrelated to underlying cancer           |
| Chronic obstructive pulmonary disease    |
| Asthma                                   |
| Pulmonary fibrosis                       |
| Congestive heart failure                 |
| Anxiety/depression                       |
| Ascites                                  |
| Chest wall deformities                   |
| Pneumonia                                |
| Pneumothorax                             |

| **TABLE 3** The Language of Dyspnea* |
|--------------------------------------|
| Diagnosis                             |
| Asthma                                |
| COPD                                 |
| Interstitial lung disease             |
| CHF                                  |
| Lung cancer                           |
| Tumor mass                            |
| Pleural effusion                      |
| Lobar/lung collapse                   |
| Metastasis                            |
| Pleural thickening                    |
| Lymphangitis                          |
| Carcinomatosis                        |
| Descriptors                           |
| My chest feels tight                  |
| I cannot get enough air               |
| My breathing requires effort          |
| I feel hunger for more air            |
| My chest feels tight                  |
| I cannot get enough air               |
| My breathing feels rapid              |
| I feel out of breath                  |
| My chest feels tightb                 |
| I cannot get enough airb              |
| My breathing is rapid                 |
| I feel out of breath                  |
| My breathing requires effort          |
| I feel out of breath                  |
| I cannot get enough air               |
| My breathing is rapid                 |
| I feel out of breath                  |
| My breathing requires effort          |
| I feel out of breath                  |
| My chest feels tightb                 |
| I cannot get enough airb              |
| My breathing requires work            |
| I feel out of breath                  |
| My chest feels tight                  |
| I feel hunger for more air            |
| My breathing requires work            |
| I feel out of breath                  |

Data from "Wilcock et al13" and "Caroci and Lareau.14"
Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.
Because dyspnea is a subjective symptom, numerous scales have been developed to quantify its description and to measure whether treatments are effective in managing the symptom.17,18 Recently, the use of a simple verbal rating scales (VRS-D) to describe dyspnea that correlate visual analogue scales were found to be reliable and easier for patients to complete.4,19 Functional assessment of dyspnea, such as the shuttle walking test,20 reading numbers aloud,21 and the UCSD Shortness of Breath Questionnaire,22 can guide clinicians to the extent that a patient’s function and therefore quality of life may be affected by their symptom of dyspnea.

**MANAGEMENT**

Treatment of dyspnea focuses on the subjective expressive nature of the complaint rather than on the biochemical markers, the rate of tachypnea, the use of accessory muscles of respiration, or the level of oxygenation in the blood. Treatment strategies include identifying underlying causes and focusing treatments toward these causes (Tables 4 and 5). General symptom control and patient comfort should focus on the specific mechanisms contributing to the dyspnea7,23–25 and on pharmacologic and nonpharmacologic measures that may enhance comfort and quality of life for cancer patients (Table 6). The mainstay of supportive

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**TABLE 4** Evaluation of Dyspnea

| Initial work-up                                    |
|---------------------------------------------------|
| History and physical examination                   |
| CBC                                                |
| Electrolytes                                       |
| Creatinine                                         |
| Chest radiograph                                   |
| Spirometry                                         |
| ECG                                               |
| Pulse oximetry                                     |

Special studies: based on presumed etiology

- Pulmonary function tests
- Exercise testing
- Chest CT
- Ventilation-perfusion lung scanning
- Gallium lung scanning
- Sinus CT
- Exercise testing
- Echocardiogram
- Nuclear medicine study
- Holter monitor
- Psychiatric evaluation

Abbreviations: CBC, complete blood count; CT, computed tomography; ECG, electrocardiogram.

**TABLE 5** Causes and Management of Dyspnea in Advanced Cancer

| Cause                                | Potential Treatment Modalities                          |
|--------------------------------------|--------------------------------------------------------|
| Obstruction of airway by tumor       | Surgery, external-beam radiation therapy, chemotherapy, |
|                                      | brachytherapy, laser therapy, corticosteroids           |
| Mediastinal obstruction              | External-beam radiation therapy, chemotherapy, corticosteroids |
| Tracheobronchial obstruction         | External-beam radiation therapy, therapeutic bronchoscopy with stent placement |
| Lung metastasis                      | Chemotherapy                                           |
| Pleural effusions                    | Thoracentesis, pleural catheter drainage, chemical pleurodesis |
| Pericardial effusions                | Pericardiocentesis; pericardial-pleural window, chemotherapy, external-beam radiation therapy |
| Superior vena cava syndrome          | External-beam radiation therapy, corticosteroids        |
| Infection                            | Antibiotics empirical, then based on culture and sensitivity |
| Pneumonia                            |                                                        |
| Aspiration                           |                                                        |
| Carcinomatous lymphangitis           | External-beam radiation therapy, chemotherapy, opioids, anxiolytics |
| Pulmonary embolism                   | Anticoagulants, caval filters                           |
| Respiratory muscle weakness          | Withraw toxic medications                              |
| Metabolic & electrolyte disturbances | Correct metabolic and electrolyte disturbances         |
| Drug related (steroid myopathy)      | Treat underlying medical conditions                     |
| Anorexia-cachexia syndrome           | Respiratory support                                     |
| Paraneoplastic disease               |                                                        |
| Other concurrent medical illnesses   |                                                        |
| (COPD, CHF, sepsis)                  |                                                        |
| Anemia                               | Blood transfusions (Hbg 8 g/L or less), recombinant human erythropoietin |

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; Hbg, hemoglobin.
treatment includes oxygen therapy, drug therapy, and general supportive therapy and counseling. 

**Oxygen**

Oxygen therapy should be tailored to the individual, with reassessment being performed on a regular and continuing basis for its usefulness in reducing dyspnea and improving overall quality of life. A recent review of the evidence supporting the use of oxygen in the palliation of breathlessness found only three small trials that lent support to its use in improving the subjective feeling of less breathlessness in cancer patients. More evidence was available for the use of oxygen in the palliation of breathlessness in COPD, and there was a lack of clear evidence for the use of oxygen in congestive heart failure.27 Because oxygen therapy can have its own adverse effects, including restriction of activities and possible impairment of quality of life, psychological dependence and difficulties withdrawing the oxygen when it is no longer clinically appropriate, and the risk of hypercapnic respiratory failure, the use of short-burst oxygen therapy for symptomatic patients with advanced cancer and breathlessness should be monitored closely. In deciding if oxygen therapy is appropriate, the N of 1 Study (Table 7) is recommended as a method of determining the benefit of this therapy.28

**Drug Therapy**

**Systemic Opioids** Systemic opioids are considered first-line therapy for the palliation of dyspnea in patients with cancer and cardiopulmonary disease.29,30 Opioid receptors are scattered throughout the respiratory tract, especially within the alveolar walls. How opioids are involved in relieving dyspnea is not well understood. Opioids may play a role in depressing the opioid receptors found in the lung, spinal cord, and central respiratory centers, reducing the anxiety experienced during episodes of dyspnea and decreasing the central perception of dyspnea. Opioids improve cardiovascular function by reducing preload to the heart, and they may also reduce ventilatory response to hypoxia and hypercapnia.31

Clinical studies clearly demonstrate that systemic opioids are an effective treatment strategy for symptomatic dyspnea with minimal side effects. What is not clearly demonstrated in these studies is optimal dosing and method of administration.32–37 Although optimal dosing is a question, doses as low as 5 mg of morphine sulfate administered subcutaneously are effective in controlling dyspnea.31 For patients receiving baseline opioids, a 25% increase in the baseline dose can relieve dyspnea for up to 4 hours,34 and sustained-release morphine administered once per day in low doses provides significant reduction in dyspnea.30 Table 8 provides a guideline for the safe use of opioids in symptomatic dyspnea.38

Opioids have an expected side-effect profile. The most common effects noted from any opioid regimen include constipation, nausea and vomiting, sedation, confusion, respiratory depression, and multifocal myoclonus.

Constipation is the most common adverse effect of the opioid analgesics. Tolerance develops slowly, if at all, to the smooth muscle effects of opioids, so that constipation usually persists when opioids are used. A regular bowel regimen that includes cathartics and stool softeners should be instituted at the

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### Table 6: Mechanisms and Symptomatic Treatment of Dyspnea

| Mechanism | Symptomatic Treatment |
|-----------|-----------------------|
| Reduce sense of effort/ improve respiratory muscle function | Energy conservation, Breathing strategies, Positioning (leaning forward), Nutrition, Inspiratory muscle exercises, Respiratory muscle rest, Medications |
| Decrease respiratory drive | Oxygen, Opiates and sedatives |
| Alter central nervous system function | Education, Psychosocial support (coping, mastery), Opiates and sedatives |
| Exercise training/ pulmonary rehabilitation | Enhance self-esteem and self-confidence, Improve efficiency of movement |

### Table 7: N of 1 Study Parameters

| Measurements | Pulse oximetry O₂, saturation, VAS score of dyspnea: baseline and during blinded treatment O₂ and air, Patient- and investigator-selected treatment of choice, Patient-rated difference between the two treatments |
| Procedure | Baseline 5 minutes—no treatment, Patient and investigators blinded to treatments, Either 5 L/min of 100% O₂ or air via face mask for 5 mins, Followed directly by 5 minutes of the alternative treatment |

Repeat the above steps six times

Abbreviations: VAS, visual analogue scale.
time the opioids are started to diminish this effect. Nausea and vomiting can occur from opioid analgesics and is markedly increased in ambulatory patients. Tolerance to this side effect generally develops within 2 to 3 days. If the symptom continues, opioid rotation and/or an antiemetic can be added. Sedation is particularly bothersome for patients who are trying to maintain their normal daily activities. Tolerance develops to this effect within several days. Confusion can result from opioid administration and should be clearly defined and separated from opioid sedative effects. Confusion, hallucinations, and acute psychosis may result from single or multiple opioid doses. If opiates are the culprit, tolerance develops to these effects. Dose adjustment and opioid rotation can be used to counteract this effect. Respiratory depression occurs most commonly in opioid-naïve patients after acute administration of an opioid and is typically associated with other signs of central nervous system depression, including sedation and mental clouding. Tolerance develops rapidly to this effect with repeated drug administration. Respiratory depression can be reversed by the opioid antagonist naloxone. Finally, high doses of all the opioid analgesics can produce multifocal myoclonus. If this effect occurs, opioid dose reduction and/or opioid rotation is recommended.

**Nebulized Opioids** Nebulized opioids have been reported by numerous authors to relieve dyspnea based on the assumption that opioids could directly affect the opioid receptors in the lungs. Nebulized opioids achieve rapid but erratic plasma levels, usually within 10 minutes, with low bioavailability. The avoidance of first-pass hepatic metabolism likely causes fewer adverse effects, such as sedation, nausea, vomiting, and confusion. A recent review of the use of nebulized opioids in COPD concluded that there is a lack of well-conducted, placebo-controlled, randomized trials using nebulized opioids for COPD, and this route of administration is not recommended. Jennings et al also concluded that there was no statistically significant effect for nebulized opioids in the management of dyspnea.

Small case studies and clinical trials have reported on the benefits of using nebulized opioids for the management of dyspnea. Coyne and colleagues reported that using nebulized fentanyl citrate improved patient perception of breathing, respiratory rate, and oxygen saturation without any adverse effects. Tanake and colleagues also showed a positive effect on dyspnea in patients with cancer who were using nebulized morphine. In other studies, nebulized opioids were reported to be no more efficacious in the treatment of dyspnea than nebulized saline, and respiratory depression has been reported with the use of inhaled opioids.

With no large clinical trials to completely resolve the question of the efficacy of inhaled opioids for the treatment of dyspnea, clinicians often rely on anecdotal evidence. For patients who are unable or unwilling to take oral opioids or who have adverse effects to the systemic administration of opioids, nebulized opioids can offer a therapeutic alternative. Nonpreserved, injectable solutions of morphine sulfate, 2.5 to 10 mg; hydromorphone, 0.25 to 1 mg; and fentanyl citrate, 25 µg diluted in 2 mL of 0.9% sodium chloride, are commonly used in the United States. Disadvantages to the use of nebulized opioids are the increased cost for supplies and equipment, the complication of the delivery system, and the inability of the patient to properly use the nebulizer.

**Anxiolytics** Because dyspnea can lead to anxiety and anxiety can exacerbate dyspnea, anxiolytics are commonly prescribed. Dudgeon et al reported anxiety is a predictor of the intensity of shortness of breath in outpatients with cancer. A recent clinical trial reported on the effectiveness of using midazolam, 5 mg every 4 hours, in addition to baseline mor-
of life, Pan et al. found that although the literature was sparse, patients with COPD may benefit from the use of acupuncture, acupressure, and muscle relaxation with breathing retraining to relieve dyspnea. Several recent studies, including one that used semi-permanent acupuncture studs in which patients applied pressure twice per day to provide ongoing stimulation to acupressure points and another using standardized acupuncture techniques, did not display effects on dyspnea for patients with advanced cancer and nonmalignant causes of dyspnea.

Psychotherapeutic support for dyspnea on face value should help ameliorate the anxiety that is frequently seen in this condition. However, a recent review of the evidence concluded that relaxation techniques for self-control and cognitive therapy to identify and challenge catastrophic cognitions have not demonstrated efficacy based on research studies available.

**CONCLUSION**

Dyspnea is a complex symptom in which central processing of information from the respiratory complex integrates into the intellectual and psychological foundations of the individual experiencing the symptom. Dyspnea is a devastating symptom in advanced cancer and advanced cardiopulmonary diseases. For patients approaching the end of life with advanced
cancer or other end-stage diseases, early and clear discussions of advanced care planning to include patient preference about interventions with increasing burdens and decreasing benefits will help direct the goals or the care and management of symptoms such as dyspnea. An evaluation should look for treatable causes of dyspnea. Palliation of symptoms with emotional support, education, and respiratory and physical therapy may all enhance quality of life. Systemic opioids are the mainstay of palliative drug therapy, the utility of which was recently confirmed in a Cochrane review. Continued ongoing research in the assessment and management of dyspnea, exercise training, and use of complementary and alternative therapies will enhance our understanding and ability to manage and treat this symptom more effectively.

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