Putting Evidence Into Practice®:
Evidence-Based Interventions for Cancer-Related Dyspnea

Wendye M. DiSalvo, RN, MSN, ARNP, AOCN®, Margaret M. Joyce, MSN, RN, AOCN®, Leslie B. Tyson, MS, APN-BC, OCN®, Ann E. Culkin, RN, OCN®, and Kathleen Mackay, RN, BSN, OCN®

Despite the common occurrence of cancer-related dyspnea, a paucity of literature is available for review, especially research literature that reports interventions to control dyspnea. The Oncology Nursing Society's Putting Evidence Into Practice® (PEP) initiative organized a team of nurses to examine the literature, rank the evidence, summarize the findings, and make recommendations for nursing practice to improve patient outcomes. Pharmacologic and nonpharmacologic agents have been used to treat dyspnea. Patients who received parenteral or oral immediate-release opioids demonstrated a benefit in the reduction of breathlessness; thus, parenteral or oral opioids are recommended for practice. Five interventions are listed in the *effectiveness not established category* and include extended-release morphine, midazolam plus morphine, nebulized opioids, the use of gas mixtures, and cognitive-behavioral therapy. This article critically examines the evidence, provides nurses with the best evidence for practice, and identifies gaps in the literature and opportunities for further research.

The Oncology Nursing Society (ONS) extended its commitment to integrate evidence into oncology nursing practice through the ONS Putting Evidence into Practice® (PEP) initiative. As a result, oncology nurses now have expanded resources that detail the best practices based on current evidence to manage or control several common symptoms encountered by patients with cancer.

Evidence typically is generated by research studies such as randomized controlled trials, meta-analyses, and integrated reviews, but other nonresearch sources such as clinical expertise, knowledge of pathophysiology, patient preferences, and cost effectiveness can contribute to the evidence base (Goode, 2000). The ONS PEP initiative targets interventions that independently fall within the scope of nursing practice or are integral to nursing care rendered in collaboration with other healthcare providers. The patient outcomes of such interventions are labeled nursing-sensitive patient outcomes and are critical to demonstrate and measure nurses' contribution to quality patient care (Given et al., n.d.).

The links between improving nursing-sensitive patient outcomes and ONS PEP evolve as ONS teams initially develop symptom measurement summaries and research existing evidence and apparent gaps in the evidence for each symptom. The evidence is separated into six categories: recommended for practice, likely to be effective, benefits balanced with harms, effectiveness not established, effectiveness unlikely, and not recommended for practice. ONS is making substantial efforts to communicate this information to practicing nurses by creating a Web-based Outcomes Resource Area (www.ons

At a Glance

- Dyspnea is a distressing and debilitating symptom for patients with cancer. The optimal treatment of dyspnea includes the use of specific therapies as appropriate to reverse the causes of dyspnea and palliative therapies to treat irreversible causes.
- Sufficient evidence shows that parenteral or oral immediate-release opioids reduce breathlessness and thus are recommended for practice. The use of oxygen therapy in hypoxic patients with cancer also showed benefit to relieve dyspnea.
- Evidence to support the use of nebulized medications to relieve dyspnea is nonconclusive. Complementary and alternative therapies, such as acupuncture and breathing retraining, also need more research to conclude effectiveness.

Wendye M. DiSalvo, RN, MSN, ARNP, AOCN®, is an advanced registered nurse practitioner at Dartmouth Hitchcock Medical Center's Norris Cotton Cancer Center in Lebanon, NH; Margaret M. Joyce, MSN, RN, AOCN®, is a nurse practitioner at the Cancer Institute of New Jersey in New Brunswick and a doctoral candidate in the College of Nursing at the University of Utah in Salt Lake City; Leslie B. Tyson, MS, APN-BC, OCN®, is a nurse practitioner and Ann E. Culkin, RN, OCN®, is a clinical nurse, both at Memorial Sloan-Kettering Cancer Center in New York, NY; and Kathleen Mackay, RN, BSN, OCN®, is a phase I research nurse at Dartmouth Hitchcock Medical Center's Norris Cotton Cancer Center. No financial relationships to disclose. (Submitted May 2007. Accepted for publication August 6, 2007.)

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.org/outcomes), producing pocket cards for each symptom that detail the evidence, and publishing the results of each evidence synthesis. This article is is part of the communication plan to disseminate evidence about nursing-sensitive patient outcomes from interventions for cancer-related dyspnea to help oncology nurses make informed clinical decisions to improve patient care and outcomes. Dyspnea was chosen as a priority symptom for the PEP initiative because it is a common symptom encountered by patients with cancer.

Dyspnea

Dyspnea has many definitions, all of which are similar and describe an uncomfortable awareness of breathing. The American Thoracic Society (1999) uses a broad definition to include the interplay of physiologic and behavioral factors and states that dyspnea is "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, social, and environmental factors, and may induce secondary physiological and behavioral responses" (p. 322). Dyspnea not only is a physical symptom but also can adversely affect quality of life (Smith et al., 2001). It is a distressing symptom for patients and a difficult one for caregivers to manage.

Dyspnea is a prevalent symptom that patients with a variety of cardiopulmonary diseases experience. In the general cancer population, dyspnea is estimated to occur in 15%–55% at diagnosis to 18%–79% during the last week of life (Ripamonti & Fusco, 2002). Dyspnea occurs in up to 60% of patients with cancer and may be caused by a tumor occluding the airway (Beckles, Spiro, Colice, & Rudd, 2003).

The causes of dyspnea in patients with cancer are many and can be attributed directly to the disease or manifestations of the disease and its treatments or be unrelated (see Figure 1). A visual analog scale (VAS) may be a useful tool in assessing the symptom of dyspnea. The optimal treatment of dyspnea includes the use of specific therapies as appropriate to reverse the causes of dyspnea as well as palliative therapies to treat irreversible causes. The nursing-sensitive interventions for dyspnea discovered through this search included two broad categories: (a) pharmacologic interventions, including oral, parenteral and nebulized opioids, other medications, and oxygen therapy, and (b) nonpharmacologic interventions, including complementary and alternative approaches.

Dyspnea Caused Directly by Cancer
Pulmonary parenchymal involvement (primary or metastatic)
Lymphangitic carcinomatosis
Intrinsic or extrinsic airway obstruction by tumor
Pleural tumor
Pleural effusion
Ascites
Hepatomegaly
Phrenic nerve paralysis
Pulmonary leukostasis
Superior vena cava syndrome

Dyspnea Caused Indirectly by Cancer
Cachexia
Electrolyte abnormalities
Anemia
Pneumonia
Pulmonary aspiration
Pulmonary emboli
Neurologic paraneoplastic syndromes

Dyspnea From Cancer Treatment
Surgery
Radiation pneumonitis or fibrosis
Chemotherapy-induced pulmonary toxicity
Chemotherapy-induced cardiomyopathy
Radiation-induced pericardial disease

Dyspnea Unrelated to Cancer
Chronic obstructive pulmonary disease
Asthma
Congestive heart failure
Interstitial lung disease
Pneumothorax
Anxiety
Chest wall deformity
Obesity
Neuromuscular disorders
Pulmonary vascular disease

Figure 1. Conditions Resulting in Dyspnea in Patients With Cancer

Note. From "Dyspnea in Cancer Patients: Prevalence and Associated Factors" by D.J. Dudgeon, L. Kristjanson, J.A. Sloan, M. Lertzman, and K. Clement, 2001, *Journal of Pain and Symptom Management, 21*(2), p. 100. Copyright 2001 by Elsevier. Reprinted with permission.

Methods and Process

A symptom measurement summary for dyspnea (Joyce & Beck, 2005) was completed and posted on the ONS Outcomes Resource Area in 2005. ONS convened a team of oncology nurses to discover and rank the existing evidence about intervention options for dyspnea. The team consisted of two advanced practice nurses (APNs), one APN doctoral student with expertise in evidence synthesis, and two oncology staff nurses. The initial work of the team was to develop an answerable question that would guide the literature search. "What can nurses do to assist patients with cancer-related dyspnea?" was chosen to narrow the focus of the evidence search to cancer-related dyspnea and to include only nursing-sensitive therapies or interventions. The question that drove the evidence search focuses solely on palliative interventions for cancer-related dyspnea. Evidence from research that considered dyspnea attributed to other etiologies may be beneficial to cancer-related dyspnea but was beyond the scope of this project.

A computerized search of bibliographic databases (MEDLINE®, CINAHL®, PsychINFO®, and the *Cochrane Database of Systematic Reviews*) using the keywords *dyspnea* or *breathlessness* focused to include the subheadings *nursing, psychology, drug therapy,* and *rehabilitation therapy* and combined with keywords *cancer* or *neoplasm* yielded 22 citations including one meta-analysis and one integrated review. All 22 citations met

the evidence inclusion criteria of research published in English that focused on nursing-sensitive interventions for relief of dyspnea in patients with cancer. A search of the National Guideline Clearinghouse and National Comprehensive Cancer Network (NCCN) yielded two dyspnea care guidelines. One guideline was excluded because the recommendations were broader than nursing-sensitive interventions; the other guideline was retained for review.

Each original article was summarized on an evidence-synthesis table by a team member and then presented to the entire team for discussion and ranking of evidence. The synthesis table noted the characteristics of the intervention: sample, setting and design, outcome measures, findings, conclusion, limitations, and ONS Levels of Evidence. The ONS Levels of Evidence (Ropka & Spencer-Cisek, 2001) are a three-tiered rankings with eight sublevels arranged from strongest (I, 1) to weakest (III, 8) level of evidence. The ONS Levels of Evidence were adapted with permission from Hadorn, Baker, Hodges, and Hicks's (1996) quality-of-evidence rating schema. Finally, when all 22 studies were reviewed and ranked, the team categorized the interventions according to the ONS PEP Weight-of-Evidence Classification Schema developed by Mitchell and Friese (n.d.). This classification schema, based on the quality of the data and confidence in the findings, categorizes interventions into six practice-relevant categories: recommended for practice, likely to be effective, benefits balanced with harms, effectiveness not established, effectiveness unlikely, and not recommended for practice. Another ONS team involved in the same PEP process but focused on a different symptom then crosschecked the dyspnea team's work to validate the evidence rankings. Lastly, the evidence synthesis table and practice recommendations were sent to four field reviewers for critique. The outcomes of the dyspnea PEP project include a short-form pocket card detailing the current evidence to manage dyspnea; a detailed version of the evidence card including references, pertinent definitions, and a synthesis table of dyspnea evidence published on the ONS Web site in the Outcomes Research area; and this article.

Highlights of Reviewed Literature

Pharmacologic Interventions

Pharmacologic and nonpharmacologic agents have been used to treat dyspnea in patients with advanced disease of any type. Nonpharmacologic agents have shown benefit; however, most patients require the additional use of pharmacologic agents.

Opioids

Oral morphine is used extensively in the palliative care setting. Other opioids, such as dihydrocodeine, codeine, and diamorphine, also are employed. A variety of doses and routes of administration have been used, but the evidence to support their use is limited to the following studies.

A systematic review published by Jennings, Davies, Higgins, Gibbs, and Broadley (2002) evaluated the use of opioids for the treatment of breathlessness in patients with terminal illnesses (see Table 1). The review evaluated 18 randomized, double-blind, placebo-controlled, crossover studies comparing the use of any opioid drug with placebo for the relief of dyspnea in patients with different diseases. The primary outcome measures were subjective measures of breathlessness evaluated by the Borg and modified Borg scales (Borg, 1982), verbal categorical scale, and VAS. The secondary outcome measure was exercise tolerance. Nine studies involved the non-nebulized route of administration and nine used the nebulized route of administration; of the nine studies using the non-nebulized route of administration, only one study was conducted in patients with cancer (Bruera, MacEachern, Ripamonti, & Hanson, 1993). Studies used varying doses of either oral or parenteral immediate-release opioids compared with placebo. The results of the meta-analysis demonstrated a strong effect of non-nebulized opioids compared with placebo in reducing breathlessness in patients with terminal illnesses. Limitations of the analysis include small sample sizes in virtually all of the studies, and only one study was conducted in patients with cancer.

Three studies that were ranked lower primarily because of small sample sizes or uncontrolled design (Allard, Lamontagne, Bernard, & Tremblay, 1999; Bruera, Macmillan, Pither, & MacDonald, 1990; Mazzocato, Buclin, & Rapin, 1999) contribute support for opioid use for the treatment of dyspnea in patients with cancer. Again, various immediate-release opioids and doses were trialed in the studies.

Mazzocato et al. (1999) conducted a randomized, double-blind, placebo-controlled trial that assessed the effects of morphine on dyspnea and respiratory function in older adult patients with advanced cancer. Nine patients were studied; seven patients were opioid naive and two were opioid tolerant. A crossover design was used; patients given morphine on day 1 were administered placebo on day 2 and vice versa. All patients were hospitalized. Morphine 5 mg subcutaneous injection was administered to opioid-naive patients; for the two opioid-tolerant patients, the regular dose of morphine was administered and, in addition, those patients were given morphine 3.75 mg by subcutaneous injection. Assessments included intensity of dyspnea by VAS and Borg ordinal scale; VAS for pain, somnolence, and anxiety; respiratory effort measured with a six-point scale; and transcutaneous pulse oximetry. Results demonstrated a significant decrease in dyspnea intensity by VAS ($p < 0.01$) and Borg scale ($p = 0.03$) with morphine compared to placebo. Pain, somnolence, anxiety, and oxygen saturation had no significant changes. The authors concluded that intermittent doses of morphine, at the doses used, reduced cancer-related dyspnea.

Bruera et al. (1990) reported results of an uncontrolled study of 20 patients with terminal cancer and dyspnea conducted to assess the effects of subcutaneous morphine on dyspnea, physical signs of respiratory failure, oxygen saturation, and expiratory concentration of carbon dioxide. All patients were admitted to a palliative care unit and all received supplemental oxygen; 15 of 20 patients were opioid tolerant, five were opioid naive. After 30 minutes of rest and immediately before the next opioid dose, dyspnea was measured by VAS, respiratory effort measured using a six-point scale, oximetry measured by arterial oxygen saturation and end tidal arterial carbon dioxide pressure, and pain measured by VAS. All patients were administered subcutaneous morphine. For opioid-tolerant patients, morphine

Table 1. Dyspnea Systematic Review and Meta-Analysis

AUTHOR	STUDY INFORMATION	CONCLUSIONS AND IMPLICATIONS	ONS LEVEL
IMMEDIATE-RELEASE OPIOIDS: ONS PEP WEIGHT-OF-EVIDENCE CATEGORY: RECOMMENDED FOR PRACTICE			
Jennings et al., 2002	This systematic Cochrane review included 18 randomized, double-blind, placebo-controlled crossover trials of opioids for the treatment of dyspnea from any cause. Patient populations were mixed. • 2 of 18 studies included cancer diagnosis only. • 1 of 18 studies included cancer with other advanced diseases. Meta-analyses were performed on all included studies and on various subgroups (e.g., nebulized opioids). Outcome measures were dyspnea and exercise tolerance.	Oral and parenteral opioids were found to be more effective than placebo in reducing breathlessness. Nebulized opioids did not appear to be effective in decreasing the sensation of breathlessness. Limitations: All but one study had a small sample (n = 6–18 subjects). Cancer-related dyspnea was included but was not a main focus of the research.	I (1)
NEBULIZED OPIOIDS: ONS PEP WEIGHT-OF-EVIDENCE CATEGORY: EFFECTIVENESS NOT ESTABLISHED			
Joyce et al., 2004	The authors analyzed 20 articles that studied the use of nebulized opioids in treating dyspnea using the ONS Levels of Evidence framework.	Not enough scientific data exist to recommend nebulized opioids for the treatment of dyspnea. Sample sizes for most of the studies were small and variables and outcome measures were heterogeneous, making it difficult to draw conclusions.	I (2)

ONS—Oncology Nursing Society; PEP—Putting Evidence Into Practice®

Note. From "Dyspnea: Meta-Analysis and Systematic Review Table," by Oncology Nursing Society, n.d. Retrieved February 27, 2008, from http://www.ons.org/outcomes/volume2/dyspnea/SystematicReviews_dyspnea.shtml. Copyright by the Oncology Nursing Society. Adapted with permission.

dose was equivalent to 2.5 times the regular opioid dose; for opioid-naive patients, a flat dose of 5 mg of morphine was administered. The average dose of morphine was 28 mg plus or minus 22 mg. Assessments of dyspnea and pain were made every 15 minutes for 150 minutes. Respiratory rate, effort, and oximetry score were measured 45 minutes after dosing. Results showed a significant decrease in dyspnea and pain after subcutaneous morphine ($p < 0.001$). Toxicity was minimal and consisted of nausea and sedation. The authors concluded that morphine appears to improve dyspnea without deterioration in respiratory function in this population, but a controlled trial with a larger sample of patients is needed to confirm the finding.

Allard et al. (1999) conducted a double-blind, randomized, continuous, sequential controlled trial to compare the efficacy of two supplementary dosing regimens of opioids on dyspnea in terminally ill patients with cancer. Eligibility criteria included patients whose dyspnea was unrelieved with rest, oxygen, or regular opioid use. Two supplementary regimens were studied; one-half of patients was administered 25% of their regular, four hourly opioid doses (total 24-hour opioid dose divided into four-hour portions) and the other half was administered 50% of their regular four hourly opioid doses. The route of administration for the supplemental opioid dose was the same as the original opioid regimen. The study was conducted at three different palliative care centers in Canada and included 33 terminally ill patients with cancer. The primary outcome variable was dyspnea intensity measured with the use of a VAS at baseline and at 30, 60, 120, 180, and 240 minutes after the supplemental dose. Respiratory frequency also was measured. Results demonstrated that the mean difference between pre- and postrandomization dyspnea intensity and respiratory frequency was 0.86 ($p < 0.0001$) and 1.56 ($p < 0.0004$), respectively. The decrease in respiratory frequency and dyspnea intensity was maintained for four hours after the supplemental opioid dose. The results strongly suggest that the two different regimens provided a similar beneficial effect on dyspnea and tachypnea and that the lower supplemental dose can be recommended. The study was the first to report a greater effect of morphine in patients with low and moderate dyspnea intensity than those with high-intensity dyspnea. The findings of the study are limited to terminally ill patients with cancer who are already receiving regular doses of opioids and whose dyspnea is not relieved with rest and oxygen supplementation.

One study (Navigante, Cerchietti, Castro, Lutteral, & Cabalar, 2006) evaluated immediate-release morphine plus midazolam, and another (Boyd & Kelly, 1997) evaluated extended-release morphine to relieve dyspnea. In both studies, the evidence is insufficient to recommend implementation.

Navigante et al. (2006) conducted a trial examining the effect of midazolam, a benzodiazepine, given in addition to morphine in terminally ill patients with cancer with severe dyspnea in the last week of life. The study was conducted in Argentina. Patients were randomly assigned (in a 1:1:1 ratio) to one of three treatment groups. The primary endpoints were dyspnea intensity as measured by a modified Borg scale and dyspnea relief (yes or no) after the intervention. The investigators also looked at the number of patients requiring rescue medication for breakthrough dyspnea and the frequency and severity of side effects of the medication used. All patients were given subcutaneous morphine and midazolam and were randomized to one of three groups: 2.5 mg morphine every four hours around the clock with midazolam rescues for breakthrough dyspnea (group MO); midazolam every four hours around the clock with morphine rescues for break-

through dypsnea (group MI); or a combination of morphine and midazolam every four hours around the clock with morphine rescues for breakthrough dypsnea (group MM). One hundred and one patients participated in the study. At 24 hours, dyspnea relief was 92% for the morphine and midazolam around-the-clock group, which was statistically significant compared to 69% ($p = 0.003$) for morphine around the clock with midazolam rescue and 46% ($p = 0.0004$) for midazolam around the clock with morphine rescue. No significant difference in dyspnea intensity was observed among the groups. Breakthrough dyspnea was observed in 34.3% given MO, 36.4% administered MI, and 21.2% given MM at 24 hours (not significant). The investigators concluded that the addition of midazolam to morphine improved control of baseline dyspnea. This was a well-conducted study; however, single blinding and the physician's knowledge of the patients' drug regimens may have influenced the need for giving rescue medication for breakthrough dyspnea. Additional data from controlled studies are needed before clinicians could recommend the use of midazolam plus morphine for dyspnea relief.

The use of extended-release morphine was not shown to be beneficial in one small study (Boyd & Kelly, 1997). The untoward effect of increased sedation, particularly at 48 hours, was reported by 4 of 15 subjects. This short-term significant adverse event made the intervention unacceptable and led to attrition from the study.

In conclusion, sufficient evidence from one meta-analysis and other studies exists to recommend the use of immediate-release morphine as beneficial in palliating the sensation of dyspnea. Toxicity was minimal, and patients experienced significant relief of a debilitating symptom. The effectiveness of morphine plus midazolam or the effectiveness of extended-release morphine to relieve dyspnea is not established by current evidence.

Nebulized Therapy

"Nebulized or aerosol therapy consists of administering a drug that is to be inhaled in a fine mist and then deposited on the respiratory tract" (McKenry & Salerno, 1992, p. 625). Theoretically, the inhalation of opioids is an appealing approach for dyspnea because it is thought that the local binding action to sensory receptors in the respiratory tract will minimize systemic toxicity. To date, however, evidence is insufficient to recommend nebulized opioid therapy for dyspnea.

Nine of 18 studies from a subgroup analysis in a meta-analysis (Jennings et al., 2002) of randomized, double-blind, placebo-controlled, crossover studies of opioids for the treatment of dyspnea in patients occurring from any condition failed to show a positive effect from nebulized opioid. Of the 18 studies, two consisted of only patients with cancer. One integrated review (Joyce, McSweeney, Carrieri-Kohlman & Hawkins, 2004) of 20 studies including experimental trials, chart reviews, and case studies that reported about the use of nebulized opioids to treat dyspnea concluded that scientific data supporting the use of nebulized opioids are lacking. This evidence synthesis recommended further research with rigorous designs and larger samples stratified according to prior opioid use.

Four individual lower-level studies also evaluated nebulized morphine, which included the use of morphine's metabolite morphine-6-glucuronide with mixed results.

A double-blinded, randomized, crossover trial (Bruera et al., 2005) compared morphine administered subcutaneously to morphine administered via nebulizer. Eleven subjects were evaluated at different time points using 0–10 self-reporting scales. Although significant dyspnea improvement was noted at the 15-minute interval in both arms ($p = 0.025$ and $p = 0.007$, respectively), no significant difference between the subcutaneous or nebulized arms was detected, which may be attributed to insufficient statistical power to detect difference in route of administration.

A small uncontrolled pilot (Tanaka et al., 1999) conducted in Japan sampled 15 patients with thoracic cancer. The patients received 20 mg of morphine in 5 ml of normal saline through an ultranebulizer. The dose was escalated to 40 mg if immediate relief did not occur. VAS was used for outcome measurement. A decrease ($p = 0.005$) in scores was noted after the nebulization. Interpretation of the study results is clouded with a possible intervention placebo effect.

Zeppetella (1997) conducted an open, uncontrolled randomized study of 17 hospice patients who received nebulized morphine (20 mg in a 2 ml saline mixture) via a facemask every four hours during a 24-hour period. Of the 17 patients, 4 were opioid naive. Multiple outcome measurements were taken at baseline and at 24 and 48 hours. One measure, the Dyspnea Quality-Quantity Score (DQQS), was significantly lower ($p = 0.0005$) at 24 hours than at baseline. Of note, the opioid-naive patients did not demonstrate benefit, thus supporting the theory of prevalence of binding receptors in airways being influenced by systemic opioids. Qualitative scores versus VAS demonstrated improvement in dyspnea sensation. No additional benefit was observed at the 24- or 48-hour time point.

Quigley, Joel, Patel, Baksh, and Slevin (2002) in a letter to the editor described one small trial of a single dose of morphine-6-glucuronide administered to nine breathless patients with cancer at dose levels of 5 mg, 10 mg, and 20 mg. All patients reported subjective improvement in breathlessness by VAS and Borg scale ($p = 0.02$) with no apparent differences among doses.

In Coyne, Viswanathan, and Smith (2002), 25 mcg of nebulized fentanyl in a 2 ml normal saline solution was used in an uncontrolled study with a convenience sample of 35 patients. Three measures showed improvement: 81% of patients reported improvement in breathing, oxygen saturation improved ($p < 0.006$), and mean respiratory rate decreased ($p < 0.02$) one hour after treatment. The unknown impact of the carrier normal saline and attrition of patients are limitations of the study. The intervention warrants further investigation.

Additional studies evaluated nebulized furosemide as a novel treatment for dyspnea in patients with cancer. In Kohara et al. (2003), 20 mg of furosemide mixed in 3 ml normal saline was administered to 15 subjects via an ultrasonic nebulizer. Effects were evaluated using the Cancer Dyspnea Scale (CDS). Results indicated a lessening of sensation according to CDS scores for sense of effort, anxiety, and total dyspnea. However, no significant change in objective data was demonstrated. Shimoyama and Shimoyama (2002) also reported the effective use of furosemide in three case studies that are ranked as low-level evidence.

In summary, scientific data about nebulized opioids is lacking in one meta-analysis and one integrated review, as well as

several lower-level studies, because of limited sample sizes or inadequate study design. The effectiveness of nebulized opioids and furosemide interventions is not established.

Oxygen Therapy

Three studies published from 1993–2003 using either oxygen therapy or gas mixtures to palliate the symptom of dyspnea were located and reviewed. The studies were limited by either sample size or design, and the effectiveness of the interventions was not established.

A prospective, double-blind crossover trial assessing the effectiveness of oxygen therapy in dyspneic hypoxic (oxygen saturation less than 90% when breathing room air for more than five minutes) patients with cancer at rest was conducted by Bruera, de Stoutz, Velasco-Leiva, Schoeller, and Hanson (1993). Patients (N = 14) were randomized to breathe oxygen or air and then crossed over to the other treatment group. Outcomes were evaluated by subjective Mini Mental State Questionnaire scores and objective pulse oximetry. Dyspnea was assessed using a VAS and respiratory rates were recorded twice for one minute, then averaged for an assigned score. Oxygen saturation, respiratory rate, and effort were significantly improved on oxygen ($p < 0.0001$). Researchers concluded that oxygen is beneficial to patients with hypoxia and dyspnea at rest. The questionable double-blind validity is a study limitation.

Bruera et al. (1993) conducted a double-blind, randomized, controlled crossover study of supplemental oxygen versus air in 33 nonhypoxic patients with cancer with dyspnea during a six-minute walk. The patients' baseline pulse, respiratory rate, or pulse oximetry level did not differ in either group. Fatigue and dyspnea were evaluated by a numerical scale (0 = absence of symptoms and 10 = worst possible symptoms). No significant differences existed among treatment groups in dyspnea at three minutes ($p = 0.78$) or in dyspnea, fatigue, and distance walked at six minutes ($p = 0.52$, 0.64, and 0.95, respectively). At this time, the routine use of supplemental oxygen in nonhypoxic patients during exercise can not be recommended.

Helium has a low density and the potential to reduce the work of breathing. A phase II trial in the United Kingdom (Ahmedzai, Laude, Robertson, Troy, & Vora, 2004) investigated the use of Heliox 28 gas mixture in patients with lung cancer with dyspnea on exertion. A double-blind randomized trial (N = 12) examined the effects of Heliox 28 compared to oxygen-enriched air and medical air on dyspnea and exercise capacity in patients with lung cancer. The study gases included Heliox 28 (72% helium and 28% oxygen), oxygen-enriched air (72% nitrogen and 28% oxygen), and medical air (78.9% nitrogen and 21.1% oxygen). Outcome measures were evaluated with VAS, modified Borg scale (0–10 with 0 indicating no symptoms and 10 the most symptoms), and continuously monitored pulse oximetry. Patients breathed the test gases in a randomized order via facemask at rest for five minutes and during a six-minute walk. After the initial five-minute inhalation, the respiratory rates were 18.5, 18.1, and 18.1 breaths per minute (Heliox 28, oxygen -nriched air, and medical air, respectively). At the completion of the six-minute walk, mean respiratory rates increased to 24.2, 25.1, and 27.2 breaths per minute (Heliox 28, oxygen-enriched air, and medical air, respectively). The increase in respiratory rate in patients after exercise was significantly lower in patients inhaling the Heliox 28 ($p < 0.001$). Oxygen saturation in those patients who received Heliox 28 had a significant improvement over the other two gas mixtures ($p = 0.0001$). Medical air and oxygen-enriched air groups had no significant differences. No adverse events were reported; the characteristic increase in voice pitch was avoided by silencing participants while breathing the gas mixtures. This small study is an inducement to further studies to establish a role for Heliox 28 therapy to improve exercise tolerance in patients with cancer-related dyspnea.

In summary, the beneficial role of supplemental oxygen to relieve dyspnea is shown in only one small study of hypoxic patients with dyspnea at rest. Insufficient data exist to recommend either Heliox 28 or supplemental oxygen therapy to improve dyspnea in nonhypoxic patients who are short of breath with exertion, and thus its effectiveness is not established.

Nonpharmacologic Interventions

Cognitive-Behavioral Approach

Cognitive refers to the ability to think and process beliefs, whereas behavior refers to what individuals do in response to everyday beliefs. Cognitive-behavioral therapy frequently is employed in the treatment of anxiety and related disorders. Patients with dyspnea often experience anxiety (Gafford & Searight, 2007). Therefore, cognitive-behavioral approaches have been trialed to determine the effect on dyspnea.

Four studies using a cognitive-behavioral intervention were reviewed; the effectiveness of cognitive-behavioral interventions is not established because of assigned lower level of evidence based on sample size or study design. All four studies occurred in the United Kingdom and were published between 1996 and 2003. Most patients had lung cancer with advanced disease, and clinical deterioration was a common phenomenon.

Three studies examined breathing retraining combined with psychosocial support interventions delivered by a trained nurse (Bredin et al., 1999; Corner, Plant, A'Hern & Bailey, 1996) or an expert palliative care physiotherapist (Hately, Laurence, Scott, Baker, & Thomas, 2003). One study was uncontrolled (Hately et al.), and the other two studies randomized patients to an intervention arm or to a control group that received the existing standard of nursing care. The intervention strategies employed in all three studies included assessing what improves and what hinders breathlessness; providing information and support for patients and families in the management of breathlessness; exploring with patients the significance of breathlessness, the disease, and their future; instructing patients in breathing control, relaxation, and distraction techniques (see Supportive Care on pp. 369–371); setting goals to enhance breathing and relaxation techniques for better function; enabling social activities and the development of coping skills; and identifying early signs of problems that need medical or pharmacotherapy intervention.

In one study of 20 patients (Corner et al., 1996), the intervention group attended weekly clinics for three to six weeks. Assessment was based on the use of a 10-point VAS (rating breathlessness at three time frames), the Functional Capacity

Scale, and the Hospital Anxiety and Depression Scale. In-depth interviews with the specialist nurse allowed patients to explore their breathlessness. The median scores on all measures were improved for the intervention group: distress from breathlessness ($p < 0.01$), breathlessness at worst ($p < 0.05$), functional capacity ($p < 0.02$), and ability to perform activities of daily living ($p < 0.03$). Anxiety or depression did not improve. The control group had a 10% increase in distress related to breathlessness compared to the intervention group.

Bredin et al. (1999) assessed the effectiveness of the same intervention in 119 patients who completed self-assessment tools at baseline and at four and eight weeks. A VAS (measuring breathlessness at worst and at best, plus distress because of breathlessness), World Health Organization (WHO) Performance Status Scale, Hospital Anxiety and Depression Scale, and Rotterdam Symptom Checklist were used to measure outcomes. At baseline, both groups reported significant distress because of breathlessness and its impact on their ability to carry out activities of daily living. At the conclusion of the study, the intervention group reported significant improvement in WHO performance status ($p = 0.02$), breathlessness at best ($p = 0.03$), degree of depression ($p = 0.02$), and physical symptom distress ($p = 0.04$). A limitation of the study was the attrition of patients.

In another study (Hately et al., 2003), a physiotherapist tested breathing retraining and psycho-educational support to reduce breathlessness. The Current Respiratory Symptoms, Functional Capacity Scale, and Sputum Production Scale were completed at each visit. The patients also completed the Rotterdam Symptom Checklist, VAS, Things That Improve Breathlessness tool, and Quality of Life Questionnaire. Qualitative data were collected and organized into themes and patterns. The study reported significant improvement in breathlessness ($p = 0.001$), anxiety ($p = 0.001$), and functional capacity ($p = 0.001$) and decrease in occurrences of dyspnea ($p = 0.001$).

Acupuncture was the cognitive behavioral approach trialed in the fourth study. Filshie, Penn, Ashley, and Davis (1996) conducted a small, open-pilot study with 20 patients to evaluate the objective and subjective use of acupuncture in patients whose breathlessness was refractory to standard medication. Acupuncture is a method of producing analgesia or altering the function of a body system by inserting fine, wire-thin needles into acupoints along a specific meridian on the body. Preceding the intervention, two dyspnea scales (a VAS and the Borg scale), the Hospital Anxiety and Depression Scale, and a VAS of pain, anxiety, and relaxation were administered. Pulse oximetry and respiratory rate were monitored, and a nurse remained with the patients for 90 minutes. The study called for minimal nurse-patient interaction unless indicated. The study reported improvement in the VAS scores of breathlessness ($p = 0.005$), relaxation, ($p < 0.005$), and anxiety ($p = 0.001$) for up to six hours. The Borg score demonstrated significant improvement in breathlessness ($p < 0.005$). The breathlessness VAS and anxiety VAS had a significant correlation ($p < 0.001$). The most significant objective change was the decreased respiratory rate sustained for 90 minutes after acupuncture ($p = 0.02$). In addition, 70% of patients reported symptomatic relief following the procedure. The intervention may have been contaminated because a nurse remained with each patient.

Table 2. Dyspnea Clinical Practice Guidelines

AUTHOR	SUMMARY OF GUIDELINES	CONCLUSIONS AND IMPLICATIONS
PALLIATIVE INTERVENTIONS TO RELIEVE CANCER-RELATED DYSPNEA: ONS PEP WEIGHT-OF-EVIDENCE CATEGORY: LIKELY TO BE EFFECTIVE		
NCCN, 2006	Clinical Practice Guidelines in Oncology™: Palliative care [v.1.2006] were developed by an expert committee based on clinical experience and available scientific evidence. All recommendations are category 2A, indicating that based on lower-level evidence, including clinical experience, a uniform NCCN consensus exists that the recommendation is appropriate.	Dyspnea management interventions are based on the following estimates of patient life expectancy. a. With years to months to live: Include symptom intensity assessment followed by treatment of underlying causes or comorbid conditions using chemotherapy or radiation therapy, thoracentesis or pleurodesis, bronchoscopic therapy or bronchodilators, diuretics, antibiotics, or transfusions. b. With a year to months to live: Include measures to relieve symptoms such as temporary ventilator support, if clinically indicated for severe yet reversible condition, and supplemental oxygen therapy. c. With months to weeks to live: Include benzodiazepines for anxiety; opioids for cough or dyspnea; nonpharmacologic therapies, including fan, cooler temperatures, stress management, and relaxation therapy; and educational, psychosocial, and emotional support. d. With weeks to days to live (dying patient): Use tachypnea or distress markers of potential dyspnea in noncommunicative patients to assess symptom intensity and focus on comfort. Include the measures listed in item c above to relieve symptoms and the following interventions. • Reduce excessive secretions with medications (scopolamine, hyoscyamine, atropine). • Use oxygen if patients indicate subjective report of relief. • Withhold or withdraw the time-limited trial of mechanical ventilation as indicated by patient and family preferences, prognosis, and reversibility. • Provide sedation as needed. • Discontinue fluid support and consider using a low-dose diuretic if fluid overload may be a contributing factor to dyspnea. • Provide anticipatory guidance for patients and families on the dying process and treatment of respiratory crisis. • Provide emotional support.

NCCN—National Comprehensive Cancer Network; ONS—Oncology Nursing Society; PEP—Putting Evidence Into Practice®

Note. From "Dyspnea: Clinical Practice Guidelines Table," by Oncology Nursing Society, n.d. Retrieved February 27, 2008, from http://www.ons.org/outcomes/volume2/dyspnea/Guidelines_dyspnea.shtml. Copyright by the Oncology Nursing Society. Adapted with permission.

In summary, breathing retraining combined with psycho-educational strategies demonstrated benefit in decreasing breathlessness in patients with lung cancer. Further investigation is needed to determine whether all of the combined strategies are needed to produce decreased dyspnea or whether one or more than one component of the intervention contributed most significantly to the positive outcome. Also, further research with a controlled design is needed to validate whether acupuncture will be an effective intervention for dyspnea.

Consensus Guideline for Dyspnea

Clinical trials that investigated specific interventions for dyspnea are limited. Hence, in the absence of sufficient data, consensus from expert clinicians, such as the National Comprehensive Cancer Network (NCCN) clinical guidelines, are considered likely to be effective. The symptom of dyspnea is considered in the guidelines on palliative care, in which the interventions are based on an estimate of life expectancy (NCCN, 2006). Table 2 displays the specific interventions adapted from the NCCN clinical guidelines.

Implications for Nursing Research

In general, the evidence cited in this article raises many clinical questions that require further research to substantiate conclusions. With few exceptions, the studies to date have not been randomized controlled trials that include sufficient subjects to demonstrate statistical significance with adequate power to show effect of the proposed intervention. A conclusion from this dyspnea evidence review is that future research should focus on increasing sample size in randomized controlled studies and stratify patients according to opioid naive or tolerant for pharmacologic studies. However, one commonality noted in the research to date is the difficulty of recruiting dyspneic patients with cancer to clinical trials because of the unstable nature of the symptom. Large-scale studies may not be feasible or may require extensive collaborative research efforts.

The cognitive-behavioral approach that trialed multiple items as one intervention for dyspnea presents an exciting research opportunity for creative nurse-specific therapies. Further research is needed to determine whether all components of the intervention are essential to produce a significant benefit or whether one or two items will achieve the same or better outcome. Another fertile area for nurse researchers is to test interventions that are known to benefit patients with dyspnea from nonmalignant causes such as chronic obstructive pulmonary disease in a cancer population.

Conclusion

Dyspnea is a distressing and debilitating symptom for patients with cancer. Efforts to identify evidence-based interventions to ameliorate the symptom and improve quality of life are paramount. Pharmacologic agents and nonpharmacologic approaches have been used to treat dyspnea in patients with cancer. Patients who received parenteral or oral immediate-release opioids demonstrated a benefit in the reduction of their breathlessness; thus parenteral or oral opioids are recommended for practice. The use of extended-release oral morphine had no benefit. Further data are needed to confirm the findings in the use of midazolam as an adjunct to morphine to move this intervention to a higher level of evidence. Evidence to support the use of nebulized medications to relieve dyspnea is nonconclusive. Although no benefit from oxygen therapy administered to nonhypoxic patients during ambulation was shown, the use of gas mixture Heliox 28 demonstrated a significant decrease in dyspnea during ambulation. The use of oxygen therapy in hypoxic patients with cancer showed benefit. Complementary and alternative therapies such as acupuncture and breathing retraining need more research to conclude effectiveness; data currently are insufficient to recommend the use of these nonpharmacologic interventions.

Oncology nurses now have expanded resources that detail best practices based on current evidence to manage or control several common symptoms including dyspnea encountered by patients with cancer. The use of the PEP cards by nurses is one way to maximize evidence-based care and positively impact outcomes for patients and families.

Author Contact: Wendye M. DiSalvo, RN, MSN, ARNP, AOCN®, can be reached at wendye.m.disalvo@hitchcock.org, with copy to editor at CJONEditor@ons.org.

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Put Evidence Into Practice

The Putting Evidence Into Practice® (PEP) resource card for dyspnea appears on the following pages. For more information about evidence-based interventions for dyspnea, including different versions of the card, definitions, evidence tables, and a complete list of references, visit www.ons.org/outcomes/volume2/dyspnea.shtml. PEP resources for several other nursing-sensitive patient outcomes are available at www.ons.org/outcomes.

The *Clinical Journal of Oncology Nursing* wants to hear how you use the PEP resources to improve the quality of cancer care that you deliver. E-mail CJONEditor@ons.org to to share your experiences with nurses everywhere.

Appendix. Putting Evidence Into Practice® Card on Dypsnea

What can nurses do to assist people with cancer-related dyspnea?

The optimal treatment of dyspnea includes using specific therapies as appropriate to reverse the causes along with using palliative therapies to treat irreversible causes for symptomatic relief. The interventions discussed in this document are palliative and are a result of a review of the literature focused solely on cancer-related dyspnea. Evidence from research that considers dyspnea attributed to other etiologies may be beneficial in cancer-related dyspnea but is beyond the scope of this document.

RECOMMENDED FOR PRACTICE

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews and for which expectation of harms is small compared with the benefits

Immediate-Release Oral or Parenteral Opioids

Evidence supports the use of oral and parenteral opioids for management of dyspnea in patients with terminal or advanced cancer because it reduces ventilatory demand by decreasing central respiratory drive. In a systematic review and several smaller studies, patients reported dyspnea relief with opioids.[1-4]

- Morphine was the predominant opioid evaluated in the studies, but other opioids also were included.
- In general, those patients who were opioid naive were given smaller doses of opioid than those who were opioid tolerant. A wide range of doses were used in the studies.
- In patients already receiving opioids on a regular basis, supplemental oral and parenteral doses consisting of either 25% or 50% of the equivalent four-hour opioid dose (e.g., total 24-hour opioid dose divided into four-hour portions) have been assessed. One study found that supplemental opioid doses 25% of the regular four-hour dose can reduce dyspnea for as long as four hours.[2]
- Overall, the opioids were well tolerated, with the exception of nausea and vomiting.
- More research is needed to define the most effective doses of oral and parenteral opioids and to determine those patients who are most likely to benefit from the use of opioids.

LIKELY TO BE EFFECTIVE

Interventions for which there is evidence from a single rigorously conducted controlled trial, consistent evidence from well-designed controlled trials using small samples or from meta-analyses/systematic reviews using small samples, or evidence from guidelines developed from evidence and supported by expert opinion

Expert consensus recommends the following palliative interventions to relieve cancer-related dyspnea.[5] The consensus guidelines for dyspnea are categorized by estimated life expectancy.

The life expectancy category labeled years to months to weeks includes the following measures to relieve symptoms:

- Temporary ventilator support if clinically indicated for severe reversible condition
- Oxygen therapy (see also supplemental oxygen evidence[6,7] listed in the Effectiveness Not Established category)
- Benzodiazepines for anxiety
  - Increasing ambient air flow directed at the face or nose such as generated by a fan
  - Providing cooler temperatures
  - Promoting relaxation and stress reduction
  - Providing educational, emotional, and psychosocial support for patients and family caregivers and referring to other disciplines as appropriate

Interventions recommended for a dying patient experiencing dyspnea include the previous measures and the following:

- Reduce excessive secretions with scopolamine, hyoscyamine, or atropine.
- Implement oxygen therapy, if subjective report of relief (see supplemental oxygen evidence[6,7] listed later in the Effectiveness Not Established category).
- Institute sedation as needed.
- Discontinue fluid support, and consider low-dose diuretics if fluid overload may be a contributing factor.

EFFECTIVENESS NOT ESTABLISHED

Interventions for which there are currently insuficient or conicting data or data of inadequate quality

Pharmacologic

Extended-Release Morphine

One small study testing the regular administration of extended-release morphine failed to show a significant reduction in dyspnea for those who completed the study.[8] In addition, out of 15 patients entered in the study, [3] withdrew because of sedation and 3 died without showing a reduction in dyspnea. The high incidence of sedation and dizziness at 48 hours after initiation should raise concern, especially in opioid-naive patients, and emphasizes the need to monitor patients carefully.[8]

Midazolam Plus Morphine

Only one trial has been reported supporting the use of the combination of midazolam* plus morphine in patients with severe dyspnea in the last week of their lives.9 This regimen cannot be recommended without more research.

Nebulized Fentanyl

Evidence is insufficient to recommend the use of nebulized fentanyl.* One small study reported a perceived benefit by the majority of patients.10 However, there were limitations to this study. Further research is needed before nebulized fentanyl can be recommended.

Nebulized Furosemide

Evidence is insufficient to support the use of nebulized furosemide* in the treatment of dyspnea. As reported by one uncontrolled study[11] and three case reports,[12] the majority of patients reported that inhalation of furosemide decreased the sensation of dyspnea. However, further rigorous research is required before this regimen can be recommended.

Nebulized Lignocaine (Lidocaine Hydrochloride)*

One small study evaluated nebulized lignocaine* in people with cancer experiencing breathlessness at rest.[13] No benefit was seen with the inhaled lignocaine. In fact, the distress of breathing increased after nebulized lignocaine.

Nebulized Opioids†

At this point, insufficient evidence exists to recommend the use of nebulized opioids in the treatment of dyspnea. Investigation into the use of inhaled nebulized opioids has yielded mixed results. Although some individual studies indicate the potential for efficacy,[14-17] higher-level reviews have failed to show positive effects of nebulized opioids for the treatment of dyspnea and recommend further research with rigorous designs and larger samples.[1,18]

Supplemental Oxygen

- In hypoxic patients experiencing dyspnea at rest, one small trial demonstrated that oxygen (which can reduce ventilatory demand) is beneficial.[6]
- For nonhypoxic dyspneic patients, the routine use of supplemental oxygen did not demonstrate benefit.7 A study looking at the use of a different gas mixture (heliox 28%) in nonhypoxic dyspneic patients undergoing exercise indicated that there may be some benefit of this gas mixture.[19]

Nonpharmacologic

Acupuncture

One study evaluated 20 patients with cancer-related breathlessness who received acupuncture.20 The patients acknowledged an improvement in their breathlessness after the acupuncture, but these results may have been contaminated by the nurse remaining with the patient for 90 minutes postintervention. Further evaluation of acupuncture for cancer-related breathlessness is indicated.

Cognitive Behavioral Approach

One multicenter and two smaller studies examined the effect of specialized nursing interventions on the quality of life of patients with lung cancer who are experiencing breathlessness.[21-23] Interventions offered in the studies included the following.

- Assessment of breathlessness—what improves and what hinders
- Provision of information and support for patients and families in the management of breathlessness
- Exploration of the significance of breathlessness with patients, their disease, and their future
- Instruction in breathing control, relaxation, and distraction techniques
- Goal setting to enhance breathing and relaxation techniques as well as to enhance function, enable participation in social activities, and develop coping skills
- Identification of early signs of problems that need medical or pharmacotherapy intervention

Patients receiving these interventions reported a significant improvement in breathlessness, emotional and physical well-being, and performance status. Further trials are needed to pinpoint which interventions are essential to improve the dyspnea outcome.

EXPERT OPINION

Low-risk interventions that are (1) consistent with sound clinical practice, (2) suggested by an expert in a peer-reviewed publication (journal or book chapter), and (3) for which limited evidence exists. An expert is an individual who has authored articles published in a peer-reviewed journal in the domain of interest.

Although limited evidence exists, experts recommend the following supportive interventions in patients experiencing cancer-related dyspnea.[24-27]

- Maximize treatments that have proven beneficial to individual patients, such as avoiding volume overload and using oxygen and nebulized bronchodilators.
- Use upright positioning that affords patients optimal lung capacity, especially with a coexisting diagnosis of chronic obstructive pulmonary disease.
- Educate patients about breathing exercises such as diaphragmatic breathing, altering breathing rhythm, and pursed lip breathing to optimize lung function.[26]
- Educate patients to recognize physical maneuvers that precipitate dyspnea. Employ interventions such as cognitive behavioral techniques (e.g., relaxation, imaging therapy) to decrease the anticipatory component associated with exertional dyspnea.
- Consider the use of assistive devices such as a wheelchair and portable oxygen to decrease physical activities that precipitate dyspnea.
- Expert opinion is conflicting regarding the use of benzodiazepines.* Some recommend it to treat anxiety associated with dyspnea,[5,24] whereas others claim that the use of an anxiolytic is not supported for relief of cancer-related dyspnea.[25,27]

* The use of this drug in the treatment of dyspnea has not been approved by the U.S. Food and Drug Administration and is considered off-label use.

† The use of the nebulized form of this drug in the treatment of dyspnea has not been approved by the U.S. Food and Drug Administration and is considered off-label use.

Authors: Wendye M. Disalvo, RN, ARNP, MS, AOCN®, Margaret M. Joyce, PhD(c), RN, AOCN®, Ann E. Culkin, RN, OCN®, Leslie B. Tyson, MS, APRN,BC, OCN®, and Kathleen Mackay, RN, BSN, OCN®

Oncology Nursing Society
125 Enterprise Drive, Pittsburgh, PA 15275
412-859-6100

Defnitions of the interventions and full citations: www.ons.org/outcomes
Literature search completed through September 2006.

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