NCPD Symptom Management Series
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Treatment of Dyspnea in Advanced Disease and at the End of Life

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Dyspnea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations, varies in intensity, and can only be known through the patient's report. Dyspnea is akin to suffocation and is one of the most distressing symptoms experienced by patients with advanced illness and at the end of life. Common approaches to dyspnea management, such as pulmonary rehabilitation, breathing strategies, or supplemental oxygen, have become accepted through pragmatic use or because studies do not include dyspnea as a measured outcome. Patients and clinicians urgently need evidence-based treatments to alleviate this frightening symptom. To fill this gap, a group of dyspnea researchers with expertise to conduct a literature review of evidence-based interventions for dyspnea in patients with serious illness produced these guidelines. We present the evidence from the strongest recommendations for practice to the weakest recommendations and include practical considerations for clinical nurses.

KEY WORDS
advanced disease, dyspnea, interventions

Dyspnea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations, varies in intensity, and can only be known through the patient's report.[1] Dyspnea is akin to suffocation and is one of the most distressing symptoms experienced by patients with advanced illness and at the end of life. The prevalence is high across diagnoses, with the greatest prevalence among patients with cardiopulmonary diseases.[2] The trajectory of dyspnea remains high in the last 90 days for patients with chronic obstructive pulmonary disease (COPD) and escalates in the last weeks for patients with lung cancer.[3] Patients across diagnoses experience an escalation in respiratory distress in the last week of life.[4]

Common management approaches for dyspnea include pulmonary rehabilitation, breathing strategies, supplemental oxygen, opioids, and nonpharmacologic strategies. Many of these approaches have become accepted through pragmatic use or because of evidence that does not include dyspnea as a measured outcome. A new clinical practice guideline focused on dyspnea in oncology will be published by the American Society of Clinical Oncology in spring 2021.[5] Other associations have previously published guidelines or statements on dyspnea.[1,6,7] However, the search criteria for those publications excluded some articles that may have a smaller sample size, specific diagnosis or setting, or lower level of evidence but still provide suggestions of dyspnea interventions of interest to palliative and hospice nurses that may prove beneficial in an "n of 1" setting with individual patients.[8] Patients and clinicians urgently need evidence-based treatments to alleviate this frightening symptom. The purpose of this review was to critique the evidence about treatment of dyspnea in the context of advanced disease and at the end of life, from the perspective of hospice and palliative care nurses with dyspnea expertise.

METHODS

The literature search was conducted in 2 stages, During stage 1, the literature from 1990 to 2015 was searched in PubMed, CINAHL, and the Cochrane Collaboration databases by a research librarian (A.Z.), and dyspnea nurse experts (M.C., D.D., E. Fahlberg, D. Thorpe, A. Walsh, L.F.R.) (Figure 1).[9] Search terms included *dyspnea*, *dyspnoea*, *breathless*, *respiratory distress*, *advanced disease*, *COPD*, *heart failure*, *lung cancer*, *dementia*, *ALS*, *end of life*, *refractory*, *opioids*, *benzodiazepines*, *bronchodilators*, *anticholinergics*, *oxygen*, *medical air*, *bipap*, *cpap*, *fans*, *positioning*, and *interventions*. The initial search yielded 486 articles from which 269 duplicates were deleted. During stage 2,

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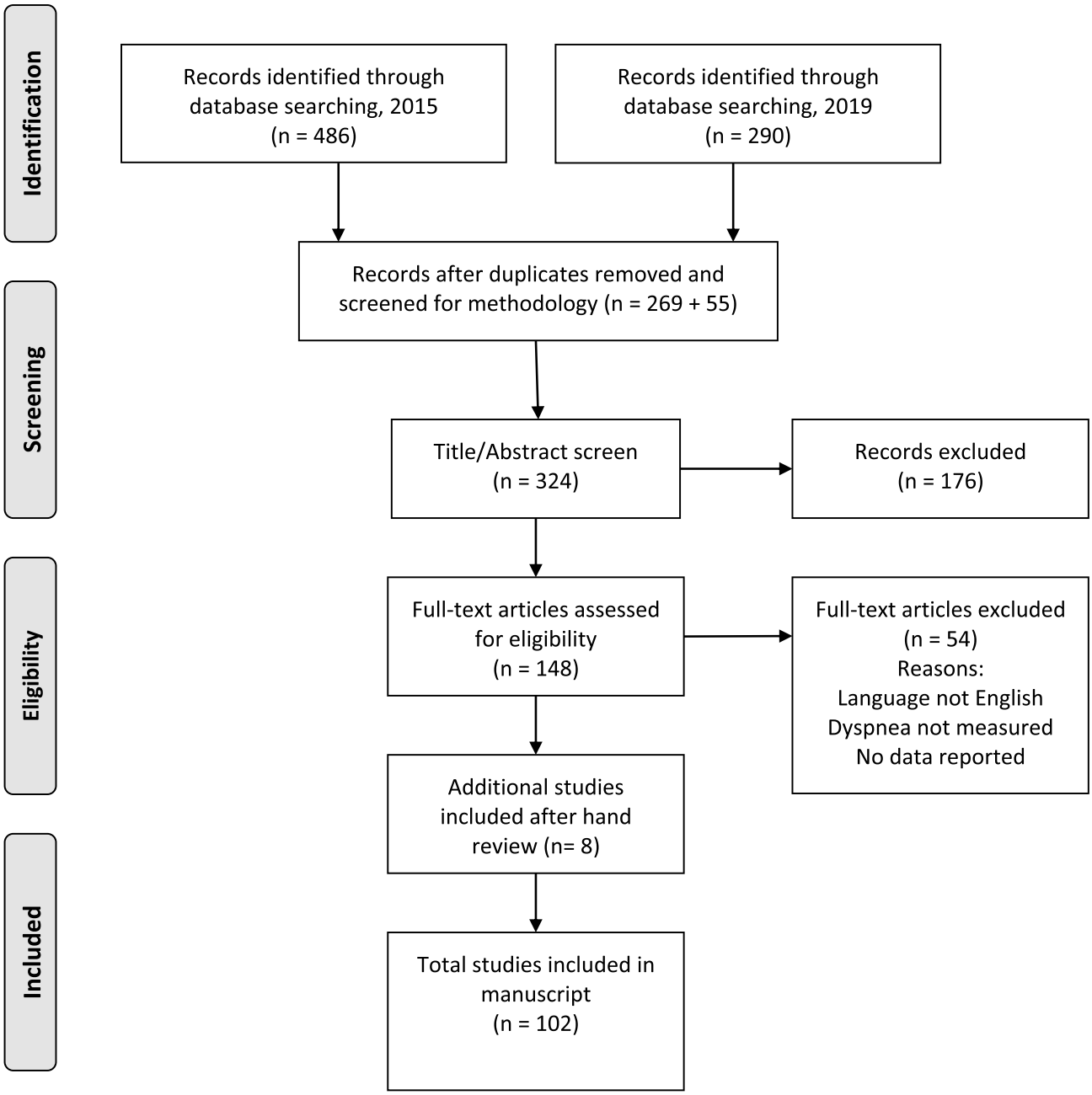

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram.

the literature from 2016 to 2019 was searched in PubMed and yielded 290 additional articles. After being hand filtered by methodology for randomized controlled trials (RCTs), systematic reviews, original research articles, and narrative reviews, 55 articles from the stage 2 search were submitted for review.

We determined that studies would be included for critique if they were full research reports, systematic reviews, or meta-analyses in which treating dyspnea was the primary or secondary study aim and dyspnea was explicitly measured. Articles that reported pilot study results when a fully powered report was available were excluded. After using these criteria in an abstract and title review, the total number of articles from both searches narrowed to 148. Following full-text review and with the addition of 8 articles that were identified through review of reference lists, 102 articles met the inclusion criteria. Levels of evidence were adapted from the Oncology Nursing Society Putting Evidence into Practice Classification (Table 1).[10]

Each article was reviewed by 2 reviewers. The intervention, comparator, location and setting, study design, population, sample size, dyspnea measure, quality of evidence, and study findings were extracted during each review and

TABLE 1 Levels of Evidence

Level of Evidence	Criteria
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
	• Supportive evidence from at least 2 well-conducted randomized controlled trials that were performed at more than 1 institutional site and that included a sample size of at least 100 participants (powered sample may be smaller in repeated measures studies)
	• Evidence from a meta-analysis or systematic review of research studies that incorporated quality ratings in the analysis and included a total of 100 patients or more in its estimate of effect size and confidence intervals
	• Recommendations from a panel of experts that derive from an explicit literature search strategy and include thorough analysis, quality rating, and synthesis of the evidence
Likely to be effective	• Interventions for which the evidence is less well established than for those listed under "recommended for practice"
	• Supportive evidence from a single well-conducted randomized controlled trial that included fewer than 100 patients or was conducted at 1 or more institutions
	• Evidence from a meta-analysis or systematic review that incorporated quality ratings in the analysis and included fewer than 100 patients or had no estimates of effect size and confidence intervals
	• Evidence from a systematic review of randomized trials that incorporated quality ratings in the analysis
	• Guidelines developed largely by consensus/expert opinion rather than primarily based on the evidence and published by a panel of experts that are not supported by synthesis and quality rating of the evidence
Balance benefit with harm	• Interventions for which clinicians and patients should weigh up the beneficial and harmful effects according to individual circumstances and priorities
	• Supportive evidence from 1 or more randomized trials, meta-analyses, or systematic reviews but where the intervention may be associated, in certain patient populations, with adverse effects that produce or potentially produce mortality, significant morbidity, functional disability, hospitalization, or excess length of stay
Effectiveness not established	• Interventions for which there are currently insufficient data or data of inadequate quality or supportive evidence from a well-conducted case-control study
	• Supportive evidence from a poorly controlled or uncontrolled study
	• Evidence from randomized clinical trials with 1 or more major or 3 or more minor methodological flaws that could invalidate the results
	• Evidence from nonexperimental studies with high potential for bias (eg, case series with comparison to historical controls)
	• Conflicting evidence but where the preponderance of the evidence is in support of the recommendation or meta-analysis showing a trend that did not reach statistical significance
Effectiveness unlikely	• Interventions for which lack of effectiveness is less well-established than for those listed under "not recommended for practice"
	• Evidence from a single well-conducted randomized trial with at least 100 participants or conducted at more than 1 site and that showed no benefit for the intervention
	• Evidence from a well-conducted case-control study, a poorly controlled or uncontrolled study, a randomized trial with major methodological flaws, or an observational study that showed no benefit and a prominent and unacceptable pattern of adverse events and serious toxicities

Continued

TABLE 1 Levels of Evidence, Continued

Level of Evidence	Criteria
Not recommended for practice	• Interventions for which ineffectiveness or harmfulness has been demonstrated by clear evidence, or the cost or burden necessary for the intervention exceeds anticipated benefit
	• Evidence from 2 or more well-conducted randomized trials with at least 100 participants or conducted at more than 1 site and that showed no benefit for the intervention; excessive costs or burden is expected
	• Evidence from a single well-conducted trial that showed a prominent and unacceptable pattern of adverse events and serious toxicities
	• Evidence from a meta-analysis or systematic review of research studies that incorporated quality ratings in the analysis and included a total of 100 patients or more in its estimate of effect size and confidence intervals with demonstrated lack of benefit or prominent and unacceptable toxicities
	• Intervention discouraged from use by a panel of experts in the related subject, after conducting a systematic examination, quality rating, and synthesis of the available evidence

Adapted from the Oncology Nursing Society.[5] Used with permission.

placed in an Excel file (Microsoft, Seattle, WA). In a series of conference calls, 6 reviewers who are expert hospice or palliative care nurses discussed each study selected during the 2015 search until consensus was reached on the quality of the evidence. For the subsequent 2019 update to the literature search, 2 authors (L.F.R., D.D.) reviewed titles and abstracts and integrated the additional articles that met the inclusion criteria into the review. Although the purpose of this article is not to provide guidelines or recommendations for practice, we organized the article from the strongest to the weakest evidence, based on the Putting Evidence into Practice Classification (Table 2).[10]

STRONG EVIDENCE

Immediate-Release Opioids

Several studies demonstrate the effectiveness of oral morphine for the treatment of acute episodic dyspnea in patients with advanced cancers, COPD, and those with chronic pain.[11-13] Oral morphine immediate release (IR) for patients with heart failure has mixed results[14] but is likely to be effective. The mechanism of action for morphine is binding to and activating the μ-opioid receptors in the central nervous system. Opioids are postulated to alter central mechanisms; in other words, opioids deceive the brain into responding to a different threshold for hypoxemia or hypercarbia and to alter volitional breathing.[15-17] A systematic review conducted by Jennings et al[11] in which 11 of the 18 studies included patients with COPD confirmed overall benefits of oral opioids compared with placebo on dyspnea. Of note, 14 of the 18 RCTs involved single dosing of opioids. Based on this evidence, oral morphine IR administered at low doses, for acute episodic dyspnea, up to 30 mg daily, is effective for dyspnea relief.

The recommendation for oral morphine and also dihydrocodeine, a semisynthetic opioid analgesic commonly used as an antitussive, is supported by findings from a systematic review comparing oral or parenteral opioids with placebo for patients with refractory breathlessness in advanced lung disease or terminal illness.[18] Among 18 RCTs, the mean change from baseline dyspnea score improved in the opioids group compared with the placebo group indicating benefit; however, dose recommendations were not provided because of significant heterogeneity among the trials.[18] Clinical guidelines recommend initiating oral doses at 5 mg (morphine equivalent) every 4 hours with an additional equivalent dose every 1 to 2 hours as needed.[19] Tolerance may develop in long-term use because of changes in opioid receptor sites including neuroadaptation and desensitization. Studies have been limited to morphine, fentanyl, and dihydrocodeine by oral and parenteral routes. Gaps remain regarding other formulations and routes, and populations other than COPD, cancer, or chronic pain.

Oxygen to Correct Hypoxemia

Oxygen is a disease-modifying treatment that corrects hypoxemia leading to a reduction in hypoxemia-induced dyspnea. Hypoxemia is understood to be an arterial oxygen tension (PaO_2) of less than 55 mm Hg or an oxygen saturation (SpO_2) of less than 85%.[20] Prior evidence among patients with COPD supports the use of supplemental oxygen to correct dyspnea in patients with chronic hypoxemia.[21,22]

Fan Directed to the Face

Fans are inexpensive and easy to use across diagnoses and settings of care, do not require a prescription, and do not induce clinician's fears regarding safety such as often occurs with the use of opioids. The mechanism of action is

TABLE 2 Summary of Interventions

Evidence	Interventions
Effective	• Immediate-release opioids
	• Oxygen to correct hypoxemia
	• Fan directed to the face
	• Long-acting bronchodilators for COPD
	• Pulmonary rehabilitation for COPD
Likely to be effective	• Sustained release or subcutaneous opioids
	• Short-acting bronchodilators for COPD
	• Breathing management techniques
	• Home-based exercise
	• Breathlessness Intervention programs
	• Acupoints and acupressure
Balance benefit with harm	• Noninvasive ventilation
	• High-flow nasal oxygen
	• Nutraceutical: coenzyme Q10
	• Acupuncture
	• Palliative bronchoscopic interventions
Effectiveness not established	• Opioid formulations, routes, diagnoses
	• Benzodiazepines
	• Oxygen without hypoxemia
	• Nebulized diuretics
	• Vaporized cannabis
	• Heliox
	• Oral steroids
	• Mindfulness training
	• Music therapy
Effectiveness unlikely	• Nebulized morphine
	• Epidural methadone
	• Oxygen without hypoxemia
	• Oxygen near death
Not effective	• Extended-release morphine in pulmonary hypertension
	• Oxycodone for chronic breathlessness
	• Opioids to improve exercise capacity

Abbreviation: COPD, chronic obstructive pulmonary disease.

unknown but postulated to be from multiple factors related to stimulation of facial temperature receptors.[23,24] Randomized trials and systematic reviews of patient perceptions constitute the evidence base in support of using a fan aimed toward the cheeks for a duration of 5 to 10 minutes for the relief of dyspnea.[25-29] A battery-operated handheld fan is convenient, or a table or wall-mounted fan may be useful when the patient cannot hold a battery-operated fan, as long as the flow is directed to the face.

Long-Acting Bronchodilators for COPD

Patients with advanced COPD are likely to be on long-acting bronchodilators when they are referred to palliative care or hospice. These agents should be continued and titrated as needed to control dyspnea and prevent episodes of acute distress.[30] Combination therapy of long-acting β-adrenergic agonists (eg, salmeterol) plus long-acting muscarinic antagonists (eg, tiotropium) provides better control than either agent alone.[31-35] Therefore, patients on a single bronchodilator without adequate dyspnea control may experience greater relief if a second type of bronchodilator is added. Hospice patients with COPD should be continued on their bronchodilators, both long-acting and short-acting, as long as possible; inhaled medications used for symptom relief are covered by the Hospice Medicare Benefit. As the patient declines and becomes unable to manipulate an inhaler, nebulized aerosol treatments provide access to the medication by breathing normally through a mouthpiece or mask without any required coordination. Evidence for the use of long-acting bronchodilators in non-COPD conditions that produce dyspnea could not be found.

Pulmonary Rehabilitation

Pulmonary rehabilitation, which includes exercise training, has become the standard of care for patients with COPD, and it has become increasingly accepted for the care of patients with dyspnea related to other serious illnesses, including interstitial lung diseases.[36] Wadell and colleagues[37] demonstrated that pulmonary rehabilitation primarily improves the affective and functional components of dyspnea, whereas the sensory component remains unchanged. Pulmonary rehabilitation is usually accessed in the presence

of moderate to severe COPD and other illnesses; the effect of exercise or pulmonary rehabilitation on dyspnea late in the disease trajectory of COPD is unknown. The long-term effects of pulmonary rehabilitation on dyspnea are also unknown. However, a systematic review and meta-analysis of 15 exercise training RCTs with patient-reported outcomes in patients with advanced cancer documented statistically significant reduction in dyspnea after 0.5 to 6 months of exercise training for the 8 RCTs (n = 564 patients) that reported on dyspnea as an outcome.[38]

LIKELY TO BE EFFECTIVE

Sustained-Release or Subcutaneous Opioids

Studies conducted by Abernethy et al[39] confirmed the effectiveness of once-daily dosing of morphine sustained release (SR) for improving refractory dyspnea and sleep and for heart failure. The mechanism of action is the same as morphine IR. The most commonly reported adverse effects are constipation, drowsiness, nausea, and vomiting. Bowel regimens including laxatives and stool softeners should be routinely prescribed to prevent constipation. There were no reports of hospitalizations for respiratory depression or decreased levels of consciousness. A recent randomized placebo-controlled trial confirmed there were no treatment-emergent adverse events from regular, low-dose morphine (SR) in patients with chronic breathlessness.[40] Morphine SR once daily is not available in the United States; therefore, 15 mg twice-daily dosing up to 30 mg is recommended.[39,41] Subcutaneous morphine for patients diagnosed with advanced lung cancer[18,42,43] is likely to be effective. A systematic review and meta-analysis found no evidence of clinically significant adverse events of opioids (varying formulations, dosages, and routes) for chronic breathlessness including respiratory depression, increase in arterial carbon dioxide tension ($PaCO_2$), increase in end-tidal carbon dioxide tension ($PEtCO_2$), decrease in PaO_2, or decrease in respiratory rate.[44] These findings may allay clinician's fear of prescribing opioids for patients with chronic breathlessness.

Short-Acting Bronchodilators for COPD

Short-acting β-adrenergic agonists (eg, albuterol) and short-acting muscarinic antagonists (eg, ipratropium) are likely to be effective in relieving dyspnea in COPD, particularly in acute symptom distress, as these are generally considered "rescue" agents. According to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines, "Short-acting inhaled β_2-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation" of COPD.[45(p98)] Therefore, these should be included in the palliative symptom management plan for acute dyspnea exacerbations.

Breathing Management Techniques

Positioning and posture are reported to be helpful for patients with dyspnea. Although respiratory mechanics are improved in the sitting position compared with supine in patients with stable heart failure, there is no difference in dyspnea.[46] A single patient training session of breathing management techniques, including breath control, pacing, relaxation, and anxiety management, may be effective for dyspnea management.[47]

Eight weeks of high-intensity interval inspiratory muscle training (IMT), supervised weekly by a physical therapist, resulted in clinically and statistically significant improvement in dyspnea as measured by the London Chest Activity of Daily Living Scale in 19 patients with advanced lung disease.[48] Patients with COPD (n = 11), interstitial pulmonary fibrosis (n = 3), bronchiectasis (n = 3), or asthma, many of them awaiting transplant, participated in 2 sessions of IMT per day with 30 fast forceful inspirations using the PowerBreathe K3 (HaB International Ltd, Southam, United Kingdom) flow resistive loading device with load starting at 50% of mean inspiratory pressure and adjusted to maintain dyspnea at 4 to 6 on the modified Borg scale during training sessions. Although a control group was not available and additional testing is necessary, these results support IMT as a viable adjunct to improve dyspnea in patients with advanced lung disease.

Home-Based Exercise

An internet-based dyspnea self-management program that included coaching for home walking has been tested with equivocal results.[49-51] The intervention included home-based exercise, nurse coaching, and dyspnea self-management administered online using chat rooms, discussion forums, and online exercise and symptoms logs.[49] Dyspnea improved within all groups, including the control group, with no difference between internet and face-to-face groups.

Patients with COPD who self-selected to purchase a lower limb cycle machine and participate in tailored self-management education experienced similar decline in dyspnea measured by the Modified Medical Research Council as that in patients in the usual exercise control group.[52] Patients in the intervention group were encouraged to use the cycle machine for at least 20 minutes per day with intensity measured by dyspnea between 3 and 4 on the modified Borg scale. No measure of exercise adherence was reported. Six-minute walk distance was maintained over 3 years for the intervention group but significantly declined in the control group. Given the tendency for patients to control their dyspnea during exercise, the increased 6-minute walk distance indicates improved functioning for the same level of dyspnea. Further study of this intervention is indicated.

Breathlessness Intervention Programs

Three UK-based breathlessness intervention programs consistently demonstrate improvement in dyspnea and distress for patients with advanced cancer and other advanced lung diseases.[53-55] These programs provide 2 to 6 home or clinic visits and telephone calls by an interprofessional team over a period of 6 weeks. Depending on the needs of the patient, the interventions include exercise prescription, breathing strategies, fan, pacing, and an action plan. An individualized Australian 6-week breathlessness intervention that included education, a handheld fan, and a written breathlessness plan documented improvement in average and worst breathlessness on a numeric rating scale (NRS) for patients with severe COPD.[56] Retrospective analysis of 45 patients with COPD who were treated in a Canadian dyspnea clinic identified 21 responders with clinically significant improvement in dyspnea as measured by Edmonton Symptom Assessment Scale at the 2-month follow-up visit.[57] The goal of the clinic was to optimize respiratory mechanics, reduce the increased drive to breathe without compromising ventilation, and improve quality of life through individualized treatment plans in patients with COPD with dyspnea despite optimal pharmacotherapy. Interventions offered through the clinic included optimization of disease-specific pharmacotherapy including comorbid treatment, opioids and oxygen therapy, referral for pulmonary rehabilitation or community-based palliative care, sleep hygiene, psychosocial support and panic control, noninvasive ventilation (NIV), and home equipment to assist with mobility and safety.

A systematic review of holistic services for breathlessness, mostly related to advanced cancer, revealed significant reductions in distress due to breathlessness as measured on the NRS.[58] Interventions included within the definition of "holistic services" included information and education related to nutrition; sleep hygiene; smoking cessation; psychosocial support; self-management strategies that included breathing techniques, emergency preparation, exercise, handheld fans, pacing, positioning, and relaxation techniques; and other interventions such as acupressure or transcutaneous electrical nerve stimulation (TENS), occupational aids, or pharmacological review. Ten studies measured breathlessness intensity with a variety of tools using various definitions of breathlessness, which prevented synthesis of the results. As health care systems in the United States are implementing chronic care management programs, breathlessness programs could serve as a care model for patients with dyspnea.

Acupoints and Acupressure

A single session of TENS over acupoints (acuTENS) produced a statistically significant improvement in dyspnea among patients with COPD compared with placebo.[59] Four weeks (20 sessions) of acupressure was associated with significant improvement in dyspnea compared with sham pressure points.[60] Although the optimal procedure, timing, and specific acupoints need to be specified, the evidence suggests that stimulating acupoints is associated with relief of dyspnea in COPD. There may be a cultural influence on the results of these studies. Studies with other disease populations could not be found.

BENEFITS BALANCED WITH HARM

Noninvasive Ventilation

Only one study was found measuring the effectiveness of NIV in a palliative context. As expected, patients with hypercarbia had a significant reduction in dyspnea.[61] Noninvasive ventilation can produce a number of adverse effects including mask intolerance, mask interference with eating, drinking and speaking, and sleep disturbance; thus, use should be goal-based and balanced with harm. In addition, if the NIV settings are not optimized to the patient's ventilation demands, dyspnea may be increased. If a short-term trial of NIV does not reduce dyspnea, other palliative alternatives should be considered.[62]

High-Flow Nasal Oxygen

High-flow nasal oxygen (HFNO) of up to 60 L/min may offer symptomatic improvement to a more diverse patient population with dyspnea because the delivery system does not cover the mouth and may affect multiple mechanisms of action.[63,64] An observational study of hospitalized patients outside of critical care revealed improved dyspnea with HFNO in 90 of 111 patients with median dyspnea visual analog scale (VAS) scores improving from 8 (6–9) prior to HFNO administration to 5 (4–6, $P < .001$) with HFNO.[65] Some patients are unable to tolerate HFNO because of skin irritation, nasal dryness, gastric distension, or epistaxis. Initiation of HFNO in patients with refractory hypoxemia will lead to subsequent patient-surrogate decisions about ceasing treatment. Home-based products are becoming available that can produce up to 30 L/min for those patients who can achieve dyspnea relief at settings lower than those achieved in the acute care setting.

Nutraceutical: Coenzyme Q10

Very few studies on the effect of nutritional supplementation on dyspnea have been published. One Italian study of coenzyme Q10 and creatine supplementation on outcomes related to COPD documented statistically significant improvements in multiple dyspnea measures after 2 months. The safety profile was not reported.[66]

Acupuncture

There was no improvement in dyspnea for acupuncture compared with placebo for advanced cancer.[67] However, 2 nonrandomized pre-post studies of acupuncture have

shown statistically significant improvement in dyspnea as part of an Edmonton Symptom Assessment Scale symptom cluster in patients with cancer[68] or those enrolled in hospice.[69] Unlike acupressure or acuTENS, acupuncture involves needles piercing the skin, which can lead to bruising, bleeding, soreness, and possibly even needles breaking off in the skin or infection if needles are not sterile. In addition, acupuncture is performed only by specially trained individuals.

Palliative Bronchoscopic Interventions

Chart review of 105 patients who received palliative bronchoscopic interventions because of benign inflammatory or malignant airway narrowing showed significant improvement in dyspnea measured by NRS immediately after the intervention.[70] Two patients experienced intraprocedural bleeding that required intensive care unit care. Other complications included temporary oxygen desaturation, stent malpositioning, edema, or delayed recovery from anesthesia.

A large RCT testing the effects of bronchoscopic lung volume reduction with Zephyr endobronchial valves (Pulmonx Corporation, Redwood City, CA) for patients with hyperinflated emphysema demonstrated statistically and clinically significant improvement in dyspnea measured by multiple validated surveys including St George's Respiratory Questionnaire, COPD Assessment Tool, and Transitional Dyspnea Inventory. Improvements in breathlessness, activity, and psychosocial parameters lasted up to 12 months.[71] Although only a select group of patients qualify for invasive lung volume reduction procedures, these results hold promise to improve quality of life for patients with emphysema.

EFFECTIVENESS NOT ESTABLISHED

Opioid Formulations, Routes, and Diagnoses

Systematic reviews of opioids for the treatment of dyspnea in patients with interstitial lung diseases include small samples of patients[72]; therefore, the effectiveness of oral morphine IR for dyspnea relief in these patients is not established. Eiser et al[73] tested the effect of diamorphine on improvement in exercise tolerance for patients with emphysema. Findings did not support the use of diamorphine for improvement of dyspnea during exercise as measured by a VAS. Nebulized fentanyl,[74] oral transmucosal fentanyl,[75] or intravenously administered fentanyl[76] has not been established to be effective for patients with advanced cancers or lung diseases. A recent retrospective study examining the effect of intravenously or subcutaneously administered fentanyl among patients with advanced cancers (n = 72) near the end of life found a significant reduction in dyspnea at rest. Controlled trials are needed to establish effectiveness.[77]

A recent study found no difference in the reduction of breathlessness now in morphine (SR) compared with placebo.[78] Both groups were allowed to take 6 doses or fewer per day of 2.5 mg morphine (IR) as needed. A group from Denmark pilot tested a morphine/hydrochlorate oral solution that contained ethanol agent compared with morphine solution without ethanol on 12 patients with advanced cancers. The morphine/hydrochlorate oral solution containing ethanol decreased breathlessness measured by the NRS within 3 minutes faster compared with the morphine solution without ethanol. The authors posit that ethanol facilitates faster absorption in the mouth.[79] These results identify the need for further studies to define the optimal dose and formulation of morphine and target populations with severe breathlessness.

Benzodiazepines

Although widely used in practice,[80] equivocal results were found with regard to benzodiazepines as a primary treatment for dyspnea.[12,43,81,82] No new evidence about benzodiazepine use to treat dyspnea in COPD and cancer was reported in a 2016 systematic review.[83] Benzodiazepines are recommended as second- or third-line treatment when opioids and other therapies have failed to relieve dyspnea.[83] Usefulness of midazolam as an adjunct to morphine was reported in a single study[84] and may be related to improvement in the anxiety related to dyspnea.

Oxygen Without Hypoxemia

Several underpowered trials of oxygen compared with medical air among patients with cancer yielded no differences in dyspnea.[85-87] Patients admitted to the hospital with acute heart failure (n = 50) were randomized to either high (≥96%) or low (90%–92%) Spo_2 targets for 72 hours with no subsequent difference in dyspnea VAS (P = .86).[88] A large multinational RCT of long-term oxygen for COPD, including the use of supplemental oxygen for exertion only, did not result in sustained benefits with regard to mortality, first hospitalization, or functional status. This study challenges the long-held belief that long-term oxygen in COPD reduced mortality; surprisingly, dyspnea was not measured.[89]

Nebulized Diuretics

Based on the review criteria, 3 articles were identified examining the use of nebulized diuretics in relieving cancer-related dyspnea. These small studies did not provide sufficient evidence to establish the effectiveness of this intervention.[90-92] A randomized crossover study of 12 healthy volunteers who inhaled 40 mg furosemide while inspiratory flow and tidal volume were controlled on a mechanical ventilator showed that the subjects experienced 20% reduction in breathing discomfort due to hypercapnia.[93]

Vaporized Cannabis

Bronchodilator effects of cannabis were reported in the 1970s, but subsequent research has not been done. A group of Canadian researchers explored the effect of

vaporized cannabis, using a commercially available vaporizing device, compared with an inert control substance and found no difference in either exertional dyspnea intensity or unpleasantness related to dyspnea in patients with COPD (n = 16).[94] Although the findings of this randomized crossover design were negative, an editorial suggests that the dosage might have been insufficient, bronchodilator medications might have blunted the effect of cannabis, or the effect might have been minimized because of participant characteristics—most had hyperinflation and stopped exercise because of leg fatigue rather than dyspnea.[95]

Heliox

Only 1 study was found in our search that explored the use of Heliox, a mixture of helium and oxygen, but the results were very promising. In an RCT, patients who received Heliox experienced improved dyspnea and improved Sa_{O_2} and were able to walk farther than with either medical air or oxygen-enriched air.[96] Given the sample size of n = 12, more research needs to be conducted to confirm the effectiveness. Heliox is not readily available outside of the critical care setting.

Oral Steroids

A Cochrane review of systemic corticosteroids for the management of dyspnea intensity, quality, and impact in patients with cancer identified 2 RCTs that compared dexamethasone to placebo (n = 114) for at least 1 week.[97] The studies indicate lower dyspnea intensity compared with placebo at 1 week for those in the intervention compared with control group, but results for quality and impact were unclear because of imprecision, inconsistency, and study limitations. The authors point out the necessity of high-quality RCTs to answer this question; in the meantime, the available evidence does not either support or reject the value of systemic corticosteroids for the treatment of dyspnea in cancer.

Mindfulness Training

Although anecdotal reports from patients are passionate in favor of mindfulness-based stress reduction (MBSR), the only RCT of MBSR documented no improvement in dyspnea either with activity or at rest.[98] A study of telephone-based mindfulness-focused acceptance and commitment therapy for patients with advanced cancer and caregivers showed similar results.[99] Given that negative adverse effects are unlikely, a trial of MBSR may be considered on an individual basis.

Music Therapy

Early evidence from 2 nonrandomized studies suggests that music therapy reduces dyspnea and other symptoms. Statistically significant improvement in dyspnea has been documented in patients with multiple diagnoses on palliative care units who experienced live flute music selected by the patient.[100] Dyspnea improvements were also demonstrated in the same population of patients who participated in a variety of music therapy activities.[101]

EFFECTIVENESS UNLIKELY

Nebulized Morphine and Epidural Methadone

Several studies including a recent systematic review have found a lack of effect of nebulized morphine[18,102-105] to reduce dyspnea. Samples included patients with advanced cancers and COPD. Thus, we conclude that nebulized morphine is unlikely to be effective in alleviating dyspnea. A pilot study testing the safety of epidural methadone[106] for patients (n = 6) diagnosed with advanced emphysema demonstrated clinical improvement in dyspnea. The small sample size prohibited detection of statistically significant improvement. In the absence of a full randomized trial, this evidence is too weak to support the effectiveness of epidural methadone.

Oxygen Without Hypoxemia and Near Death

Palliative oxygen versus medical air was tested in a multinational RCT of patients with life-limiting illness, refractory dyspnea, and no hypoxemia. No differences in dyspnea were found.[107] Similarly, among a sample of patients who were near death and in no respiratory distress, oxygen was withdrawn with no change in respiratory comfort.[108]

WEAK EVIDENCE

Extended-Release Morphine for Pulmonary Arterial Hypertension

A single, randomized controlled, double-blind, placebo-controlled crossover trial of extended-release morphine for pulmonary arterial hypertension was done. The findings favored placebo for beneficial effects on dyspnea, and morphine generated more harm including nausea and constipation.[109] Extended-release morphine is not indicated for dyspnea relief in patients with pulmonary arterial hypertension.

Oxycodone for Chronic Breathlessness

A multisite, randomized, placebo-controlled clinical trial of oral controlled-release oxycodone (5 mg every 8 hours) was conducted in patients with chronic breathlessness.[110] The results found no difference in the rating of breathlessness intensity compared with placebo; therefore, oxycodone is not recommended.

Opioids to Improve Exercise Capacity

A systematic review conducted on the effect of opioids (varying formulations and doses) on breathlessness and exercise capacity in patients with COPD demonstrated a

reduction in breathlessness but no improvement in exercise capacity.[111]

DISCUSSION

The evidence specific to dyspnea relief is very limited for the majority of interventions commonly used to manage dyspnea. Consequently, clinicians often use anecdotal evidence or interventions shown to improve the mechanisms of disease when recommending dyspnea relief interventions for their patients. Effective dyspnea relief is dependent on self-management and complementary interventions. Of the interventions most likely to be effective for dyspnea relief, only morphine, oxygen, inhalers, and interprofessional programs such as pulmonary rehabilitation and breathlessness interventions services are prescribed by a provider. Other interventions such as fans, breathing strategies, and acupressure can be accessed independently by patients and caregivers; however, education about these interventions is usually offered by a clinician.

Among pharmacological treatments, oral morphine is effective and safe in reducing acute episodic and chronic refractory dyspnea for patients with advanced lung diseases including COPD and lung cancer and in patients with heart failure. Clinical guidelines recommend beginning morphine at low doses for patients who are opioid-naive and titrating to achieve a balance of benefit with few adverse effects. Starting dose of immediate release morphine

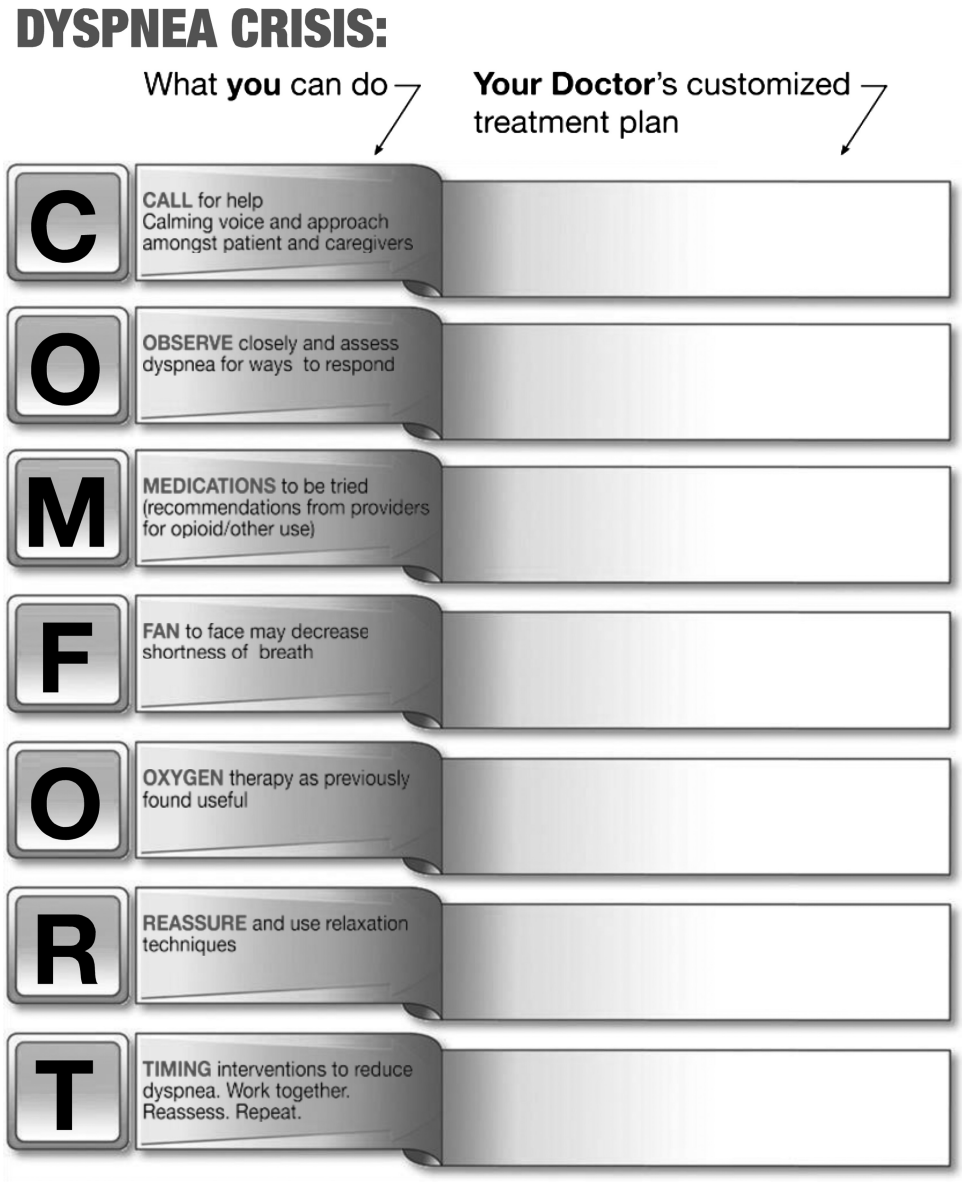

FIGURE 2. Customizable caregiver plan for episodes of crisis dyspnea. Used with permission from the American Thoracic Society (August 12, 2020).

is 5 mg every 4 hours up to 30 mg/d and for SR 15 mg twice daily up to 30 mg/d. Common adverse effects include constipation, drowsiness, nausea, and vomiting. Bowel regimens should be routinely ordered to prevent constipation. Nebulized morphine is not effective in alleviating dyspnea. Patients and clinicians may be hesitant to initiate trials of morphine because of its addictive properties and potential to induce respiratory distress. Explaining the difference in dosing compared with pain management and studies reporting the lack of evidence of respiratory depression may mitigate concerns.

Oxygen use is a topic that stimulates much interest among hospice and palliative nurses and patients. The evidence supports the use of oxygen for dyspnea relief in patients who are hypoxic, but patients who are not hypoxic seem to experience as much dyspnea relief from medical air by nasal cannula as from supplemental oxygen. High-flow oxygen may provide some dyspnea relief, but the availability in the home setting is limited, and the benefit must be balanced with the potential discomfort of skin irritation, nasal dryness, gastric distension, or epistaxis. The effectiveness of Heliox has not been established, and it is not readily available outside of the critical care setting. Together, these findings suggest that oxygen may provide dyspnea relief in specific situations, but the goals of treatment and the patient's personal priorities are important considerations when deciding whether to include oxygen in the plan of care.

Pulmonary rehabilitation and exercise-based interventions have the strongest evidence within the category of nonpharmacologic dyspnea relief. The evidence is consistent and paradoxical—exercise training causes short-term increases in dyspnea, but if a person can cope with the dyspnea and continue exercise training over time, their physical fitness increases, they become less deconditioned, their functional reserves increase in respect to their daily activities, and their experience of dyspnea decreases in relationship to their usual daily activities.[112] In addition, the fear and distress related to dyspnea—their "affective response" to the symptom decreases, possibly through desensitization.[113] The positive effect of exercise on dyspnea has been demonstrated in formal pulmonary rehabilitation programs and also in-home exercise and holistic breathlessness interventions.

Given the unrelenting distress caused by dyspnea for people with serious and chronic illnesses, patients often search beyond traditional medical care for symptom relief. Interventions focused on acupoints, breathing strategies, music, and mindfulness all have enthusiastic anecdotal support, but the studies tend to be underpowered or nonexistent. These interventions are unlikely to cause serious adverse effects or complications, so "n of 1" trials while monitoring the patients for any potential unforeseen negative consequences make sense.[8] Nutritional supplementation and nebulized cannabis are topics that deserve additional exploration. A 2012 volume on integrative therapies for people with lung disease provides additional exploration of nonpharmacologic therapies that may benefit patients with dyspnea.[114]

Many of the studies of nonpharmacologic interventions for dyspnea are limited by very small sample sizes. The lack of evidence in support of some dyspnea interventions may indicate that the research has not been done, rather than ineffectiveness an intervention. Given the dearth of effective evidence-based interventions for dyspnea, patients often find the most benefit by joining online or in-person support groups such as the American Lung Association's Better Breathers groups or EFFORTS (emphysema.net) and share strategies with each other that they find to be effective.

Music therapy is a benign intervention that lacks a strong evidence base. A number of rigorous trials have found effectiveness about music for pain relief; music may have a role for treating other symptoms such as dyspnea.[115] A well-designed study on the effect of music on anxiety in ventilated critically ill patients could serve as a model for studying the effect of music on dyspnea.[116]

Application to Nursing Practice

Dyspnea is a debilitating symptom for patients and their caregivers and can escalate near the end of life. Acute episodes of "dyspnea crisis" are defined as a "sustained and severe resting breathing discomfort that occurs in patients with advanced, often life-limiting illness and overwhelms the patient and caregivers' ability to achieve symptom relief."[117] Dyspnea crisis may result in overutilization of health care resources and requires individual and system-based approaches directed at prevention and early management. The American Thoracic Society statement provides an approach using a mnemonic "COMFORT" that can be adapted by patients and caregivers and practiced in advance, to minimize the panic of managing a dyspnea crisis[118] (Figure 2).

LIMITATIONS

The level of evidence available for many studies of dyspnea interventions is limited by sample size. The effect of disease mechanisms versus the common pathway of dyspnea sensation has not been delineated.[119] Interventions may be specific to diagnoses, and others may affect the common pathway of dyspnea. Some intervention studies with dyspnea as the outcome of interest may have been missed by our search strategy. Many dyspnea interventions have only been tested in limited samples, often patients with COPD and cancer. Gaps remain regarding the effectiveness of many interventions in other diagnoses and populations. Interventions need to be tested over time in multiple dyspnea-causing diagnoses across the continuum of illness.

CONCLUSION

Dyspnea causes severe distress in patients with advanced stage illness. Our understanding of interventions to relieve dyspnea lags behind our understanding of dyspnea mechanisms and interventions for other symptoms such as pain. Recent developments in dyspnea measurement facilitate quantification of multidimensional dyspnea experience with very little patient or provider burden. Recognition of the value of dyspnea-specific interventions and addition of dyspnea measurement in studies of palliative and cardiopulmonary interventions would enhance the knowledge base for treating this distressing symptom.

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