ASCO special articles

Management of Dyspnea in Advanced Cancer: ASCO Guideline

David Hui, MD[1]; Kari Bohlke, ScD[2]; Ting Bao, MD[3]; Toby C. Campbell, MD, MS[4]; Patrick J. Coyne, MSN, ACHPN, ACNS-BC[5]; David C. Currow, BMed, MPH, PhD[6]; Arjun Gupta, MD[7]; Aliza L. Leiser, MD[8]; Masanori Mori, MD[9]; Stefano Nava, MD[10]; Lynn F. Reinke, PhD, ARNP[11]; Eric J. Roeland, MD[12]; Carole Seigel, MBA[13]; Declan Walsh, MD, MSc[14]; and Margaret L. Campbell, PhD, RN[15]

abstract

PURPOSE To provide guidance on the clinical management of dyspnea in adult patients with advanced cancer.

METHODS ASCO convened an Expert Panel to review the evidence and formulate recommendations. An Agency for Healthcare Research and Quality (AHRQ) systematic review provided the evidence base for nonpharmacologic and pharmacologic interventions to alleviate dyspnea. The review included randomized controlled trials (RCTs) and observational studies with a concurrent comparison group published through early May 2020. The ASCO Expert Panel also wished to address dyspnea assessment, management of underlying conditions, and palliative care referrals, and for these questions, an additional systematic review identified RCTs, systematic reviews, and guidelines published through July 2020.

RESULTS The AHRQ systematic review included 48 RCTs and two retrospective cohort studies. Lung cancer and mesothelioma were the most commonly addressed types of cancer. Nonpharmacologic interventions such as fans provided some relief from breathlessness. Support for pharmacologic interventions was limited. A meta-analysis of specialty breathlessness services reported improvements in distress because of dyspnea.

RECOMMENDATIONS A hierarchical approach to dyspnea management is recommended, beginning with dyspnea assessment, ascertainment and management of potentially reversible causes, and referral to an interdisciplinary palliative care team. Nonpharmacologic interventions that may be offered to relieve dyspnea include airflow interventions (eg, a fan directed at the cheek), standard supplemental oxygen for patients with hypoxemia, and other psychoeducational, self-management, or complementary approaches. For patients who derive inadequate relief from nonpharmacologic interventions, systemic opioids should be offered. Other pharmacologic interventions, such as corticosteroids and benzodiazepines, are also discussed.

Additional information is available at www.asco.org/supportive-care-guidelines.

J Clin Oncol 39:1389-1411. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 8, 2021 and published at ascopubs.org/journal/jco on February 22, 2021: DOI https://doi.org/10.1200/JCO.20.03465

Practice Guidelines Committee approval: November 20, 2020

Reprint Requests: 2318 Mill Road, Suite 800, Alexandria, VA 22314; guidelines@asco.org

INTRODUCTION

Dyspnea, also known as breathlessness or air hunger, is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity[1] (see Table 1 for a list of definitions). It is one of the most common and distressing symptoms affecting patients with advanced cancer.[2] In a meta-analysis that included more than 10,000 patients with advanced cancer, 10%-70% of patients reported dyspnea.[2] Dyspnea typically increases in prevalence and intensity as patients approach the last weeks to days of life.[3-6] In a longitudinal observational study of patients with lung cancer, dyspnea was consistently ranked as the most distressing symptom.[7] The burden of dyspnea is further compounded by other related symptoms such as fatigue, anxiety, and depression, resulting in functional limitation, compromised quality of life, and increased informal (family) caregiver burden.[8] In the advanced cancer setting, the presence of dyspnea, particularly at rest, indicates a poor prognosis (typically less than a few months) and has important clinical implications.[9] First, a patient's prognosis could significantly affect recommendations regarding assessments and treatments. Second, clinicians need to routinely engage in serious illness conversations with the patients and their caregivers to ensure prognostic understanding, discuss how dyspnea should be managed (eg, cancer treatments and palliative options), and support advance care planning.

THE BOTTOM LINE

Management of Dyspnea in Advanced Cancer: ASCO Guideline

Guideline Question

How should dyspnea be managed in adult patients with advanced cancer?

Target Population

Adult patients with advanced cancer and dyspnea.

Target Audience

Clinicians who provide care to adult patients with cancer, as well as patients and informal (family) caregivers.

METHODS

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the clinical literature.

Recommendations

1. Screening and assessment
   - 1.1. Clinicians should perform systematic assessment of dyspnea at every inpatient and outpatient encounter in patients with advanced cancer using validated patient-reported outcome measures (good practice statement).
   - 1.2. For patients who are unable to self-report, clinicians should use a validated observation measure (good practice statement).
   - 1.3. Whenever possible, patients with dyspnea should undergo a comprehensive evaluation for the severity, chronicity, potential causes, triggers, and associated symptoms, as well as emotional and functional impact (good practice statement).

Note. Examples of validated and easy-to-use assessment tools are provided in the Data Supplement, online only.

2. Treatment of underlying causes
   - 2.1. Patients with potentially reversible, common etiologies of dyspnea such as pleural effusion, pneumonia, airway obstruction, anemia, asthma, chronic obstructive pulmonary disease (COPD) exacerbation, pulmonary embolism, or treatment-induced pneumonitis should be given goal-concordant treatment(s) consistent with their wishes, prognosis, and overall health status (good practice statement).
   - 2.2. Patients with dyspnea because of underlying malignancy (eg, lymphangitic carcinomatosis, atelectasis because of large pulmonary mass, malignant pleural effusion) may benefit from cancer-directed treatments if consistent with their wishes, prognosis, and overall health status (good practice statement).
   - 2.3. Patients with underlying comorbidities such as COPD or heart failure should have the management of these conditions optimized (good practice statement).
3. Referral to palliative care
   - 3.1. Patients with advanced cancer and dyspnea should be referred to an interprofessional palliative care team where available (type: evidence based; evidence quality: intermediate; strength of recommendation: strong).
4. Nonpharmacologic interventions
   - 4.1. Airflow interventions such as directing a fan at the cheek (trigeminal nerve distribution) should be offered (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).
   - 4.2. Standard supplemental oxygen should be available for patients with hypoxemia who are experiencing dyspnea (ie, $SpO_2 \leq 90\%$ on room air) (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).
   - 4.3. Supplemental oxygen is not recommended when $SpO_2 > 90\%$ (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).
   - 4.4. A time-limited therapeutic trial of high-flow nasal cannula oxygen therapy, if available, may be offered to patients who have significant dyspnea and hypoxemia despite standard supplemental oxygen (type: evidence-based; evidence quality: low; strength of recommendation: moderate).
   - 4.5. A time-limited therapeutic trial of noninvasive ventilation, if available, may be offered to patients who have significant dyspnea despite standard measures and do not have contraindications (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

4.6. Other nonpharmacologic measures such as breathing techniques, posture, relaxation, distraction, meditation, self-management, physical therapy, and music therapy may be offered (type: evidence-based; evidence quality: low; strength of recommendation: weak).
4.7. Acupressure or reflexology, if available, may be offered (type: evidence-based; evidence quality: low; strength of recommendation: weak).
4.8. Evidence remains insufficient for a recommendation for or against pulmonary rehabilitation in patients with advanced cancer and dyspnea.

5. Pharmacologic interventions
5.1. Systemic opioids should be offered to patients with dyspnea when nonpharmacologic interventions are insufficient to provide dyspnea relief (type: evidence-based; evidence quality: low; strength of recommendation: moderate).
5.2. Short-acting benzodiazepines may be offered to patients who experience dyspnea-related anxiety and continue to experience dyspnea despite opioids and other nonpharmacologic measures (type: evidence-based; evidence quality: low; strength of recommendation: weak).
5.3. Systemic corticosteroids may be offered to select patients with airway obstruction or when inflammation is likely a key contributor of dyspnea (type: evidence-based; evidence quality: low; strength of recommendation: weak).
5.4. Bronchodilators should be used for palliation of dyspnea when patients have established obstructive pulmonary disorders or evidence of bronchospasm (type: evidence-based; evidence quality: low; strength of recommendation: weak).
5.5. Evidence remains insufficient for a recommendation for or against the use of antidepressants, neuroleptics, or inhaled furosemide for dyspnea.
5.6. Continuous palliative sedation should be offered to patients with dyspnea that is refractory to all standard treatment options and all applicable palliative options, and who have an expected life expectancy of days (type: informal consensus; evidence quality: low; strength of recommendation: moderate).

Note. Table 2 and Figures 1-3 illustrate how these management strategies can be applied in different settings.

Additional Resources

More information, including a supplement, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

The purpose of this guideline is to provide evidence-based recommendations for the management of dyspnea in patients with advanced cancer. Similar to pain, chronic dyspnea is a multidimensional construct with physical, emotional, and social components.[1,10] Thus, a variety of pharmacologic and nonpharmacologic therapies are needed to address the multidimensional sources of suffering.

This ASCO clinical practice guideline is formulated based on a recently completed systematic review supported by the Agency for Healthcare Research and Quality (AHRQ)[11,12] and provides practical recommendations taking into account the clinical context as well as risks and benefits of each intervention with input from an interprofessional group of expert clinicians and researchers.

It is important to note that few adequately powered randomized controlled trials (RCTs) on dyspnea in the advanced cancer setting have been conducted. These studies are particularly difficult to complete because the patients with advanced cancer and dyspnea are often in distress and have a poor performance status and short survival. The paucity of high-quality data, coupled with variability in trial design, study interventions, and outcomes, poses a challenge to formulating a set of recommendations when more evidence is often needed. Where appropriate, data from other patient populations may be discussed and will be explicitly stated.

A hierarchical approach to dyspnea is recommended, beginning with ascertaining if there are potentially reversible causes, followed by the use of nonpharmacologic interventions, with pharmacologic interventions as the final additions to a treatment plan (Figs 1-3). In this guideline, we discuss interventions in descending order from nonpharmacologic to pharmacologic and from most benefit with least adverse effects to those with more potential adverse effects.

GUIDELINE QUESTIONS

This clinical practice guideline addresses five clinical questions: (1) how should dyspnea be assessed in patients

TABLE 1. Definitions

Term	Definition
Advanced cancer	The American Cancer Society defines advanced cancer as cancers that cannot be cured, and metastatic cancer as tumors that have usually spread from where they started to other parts of the body.[180] However, not all advanced cancers are metastatic. For example, brain tumors may be considered advanced because they are often not curable, even in the absence of metastasis.[1] In this guideline, particular emphasis was placed on studies including patients with advanced cancer. Other patient populations were also considered when formulating the recommendations.
Dyspnea	The American Thoracic Society defines dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity." In this guideline, dyspnea is considered to be equivalent to breathlessness and air hunger.[1]
High-Flow Nasal Cannula (HFNC)	Delivers a humidified, heated, air oxygen blend (allowing from 21% to 100% fraction of inspired oxygen) generating up to 60 L/min flow rates through a large-diameter nasal cannula.
Hypercapnia	$PaCO_2 \geq 45$ mmHg
Hypoxemia	Oxygen saturation (SpO_2) $< 90\%$ while breathing room air at rest, which is equivalent to PaO_2 of < 60 mmHg.
Morphine-equivalent daily dose (MEDD)	The total dose of opioid use per 24-hour period, taking into account both the scheduled and rescue doses. To facilitate this calculation, different opioids can be converted to oral morphine equivalents using standardized ratios. Fifteen milligram of oral morphine is equivalent to 3.75 mg of oral hydromorphone, 5 mg of oral oxymorphone, 10 mg of oral oxycodone, and 15 mg of hydrocodone.[181] Parenteral opioids are generally 2-3× as strong as their oral counterparts.
Noninvasive ventilation	The American Thoracic Society and European Respiratory Society Guideline defines noninvasive ventilation as "noninvasive variable positive airway pressure (most commonly 'bilevel') devices consisting of a higher inspiratory positive airway pressure and a lower expiratory pressure as well as continuous positive airway pressure (CPAP) delivered using various nasal, oronasal, and facial interfaces."[182(p2)]
Standard supplemental oxygen	Conventional oxygen therapy delivered via nasal cannula or face masks, which can achieve flow rates of up to 15 L/min.

with advanced cancer? (2) what underlying conditions cause or contribute to dyspnea and warrant specific management? (3) what is the role of palliative care in the management of dyspnea? (4) what nonpharmacologic interventions provide palliation of dyspnea? (5) what pharmacologic interventions provide palliation of dyspnea?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met via teleconference and/or webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the guideline was provided by ASCO. Funding for the AHRQ systematic review was provided by the Patient-Centered Outcomes Research Institute (PCORI).

For the questions on dyspnea assessment, management of underlying conditions, and the role of palliative care in the management of dyspnea (questions 1-3), PubMed and the Cochrane Library were searched through July 31, 2020, with no restriction on start date. Articles were selected based on the following criteria:

- Population: patients ≥ 18 years of age with advanced cancer (unlikely to be cured or controlled with treatment) and breathlessness.
- Interventions: assessment of dyspnea, management of underlying conditions, and specialty palliative care or breathlessness services.
- Study designs: systematic reviews, clinical practice guidelines, and RCTs.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews, or RCTs included in eligible systematic reviews; or (3) published in a non-English language.

Definitions of key terms are provided in Table 1. Search terms are provided in the Data Supplement. When little or no direct evidence was available, the panel considered the

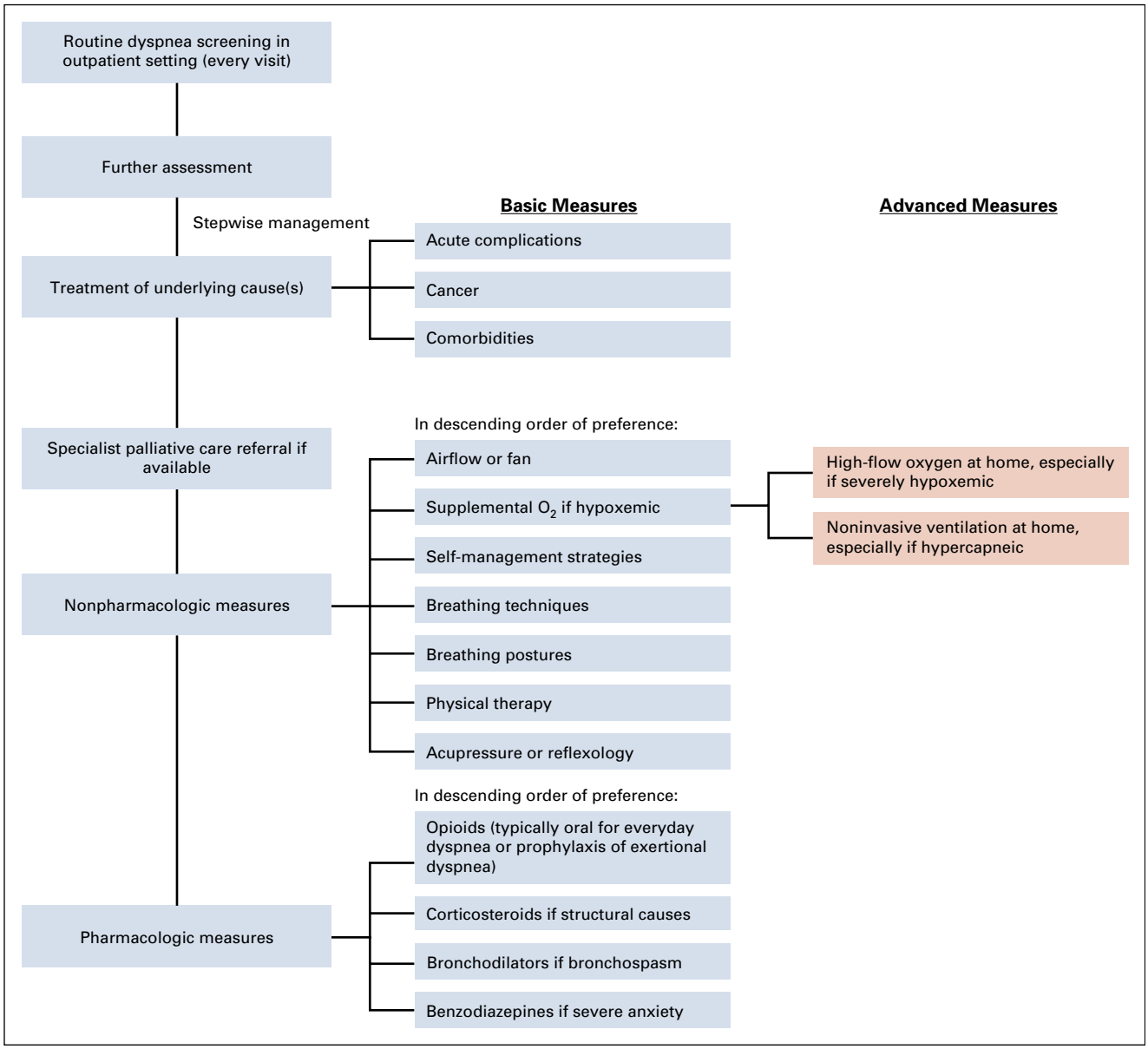

FIG 1. Outpatient management of chronic dyspnea. In the ambulatory setting, patients may present with chronic dyspnea that may limit their daily activities. A hierarchical approach is recommended to introduce interventions in a stepwise manner to include treatment of reversible causes, a palliative care consultation, nonpharmacologic measures, and pharmacologic measures. Opioids, if required, are mostly available in oral route, although subcutaneous route is also possible. Regularly scheduled opioids may be useful for everyday dyspnea and prophylactic opioids may be considered before exertion. Although home versions of high-flow nasal cannula and noninvasive ventilation are not to be routinely provided, they may be appropriate for selected individuals (light orange).

appropriateness of providing good practice statements based on discussion and criteria provided by the GRADE Working Group.[13] The ASCO guidelines program has not yet fully transitioned to using GRADE for guideline development, but this effort represents a step in that direction. Good practice statements are recommendations that are important and actionable but not appropriate for formal ratings of the quality of the evidence.[13]

The evidence base for the recommendations on the treatment of dyspnea was provided by the AHRQ systematic review.[11,12] PubMed, Embase, CINAHL, ISI Web of Science, and the Cochrane Central Register of Controlled Trials were searched through early May 2020, with no restriction on start date. Articles were selected based on the following criteria:

- Population: patients ≥ 18 years of age with advanced cancer (unlikely to be cured or controlled with treatment) and breathlessness. Restricted to studies in which at least half of the patients had cancer or studies that provided cancer-specific results.
- Interventions: nonpharmacologic or pharmacologic interventions for the palliation of dyspnea.

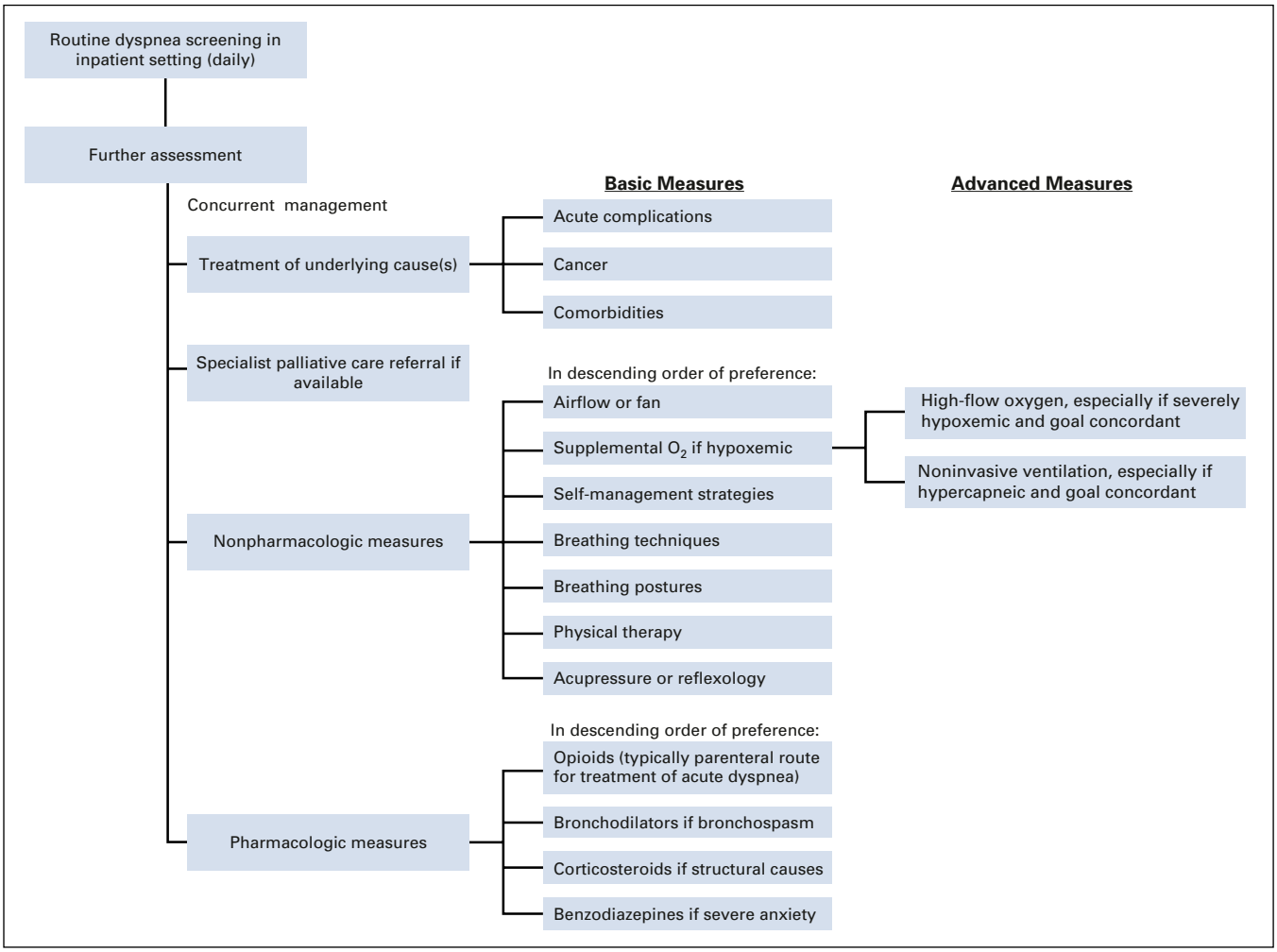

FIG 2. Inpatient management of acute severe dyspnea. In the hospital setting, patients may report acute dyspnea, which requires more urgent attention. Instead of a stepwise trial, clinicians may consider a concurrent approach to treat any reversible causes while providing palliation. Under close monitoring, patients could try different interventions and identify the most effective strategies. Medications may be given parenterally for rapid treatment of dyspnea. Supplemental oxygen, including high-flow nasal cannula and noninvasive ventilation, may be necessary for patients with hypoxemic or hypercapnic respiratory failure.

- Study designs: RCTs and observational studies with concurrent comparison groups.
- Sample size: ≥ 10 patients per arm.

Articles were excluded from the systematic reviews if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; (3) published in a non-English language.

The guideline recommendations were crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.[14] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

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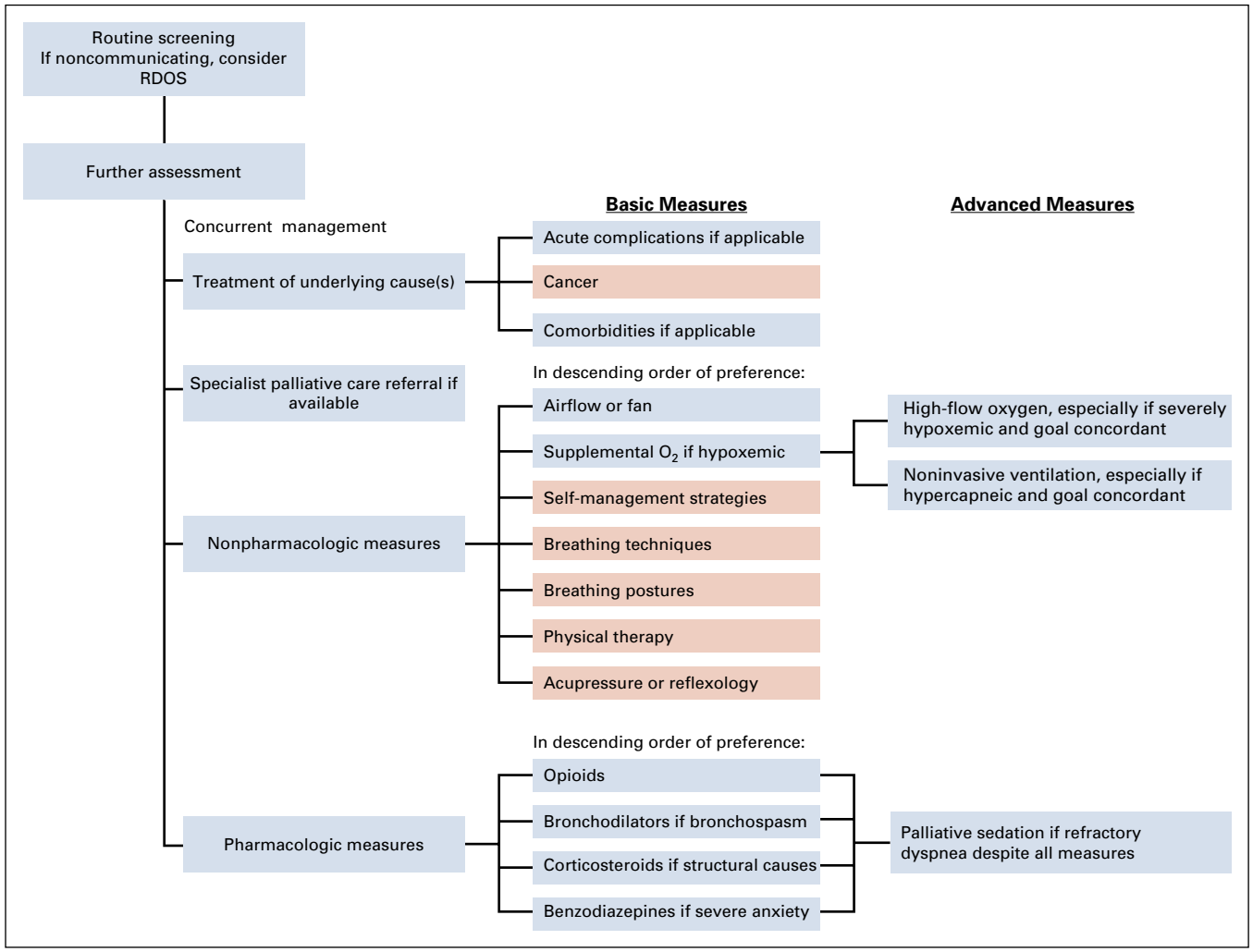

FIG 3. Inpatient management of patients with dyspnea in the last days of life. Patients in the last days of life often have severe dyspnea requiring hospitalization. A palliative care consultation is essential. Delirium and drowsiness may complicate symptom assessment and goals-of-care discussions. The short life expectancy increases the urgency to alleviate dyspnea and may limit the role of other therapies, such as cancer treatments, self-management strategies, and physical therapy (light orange). Palliative sedation is a potential option for highly selected patients with refractory dyspnea. RDOS, Respiratory Distress Observation Scale.

may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating clinician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an as is basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel

completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The review conducted for the first three clinical questions (assessment of dyspnea, management of reversible causes of dyspnea, and referral to palliative care and/or specialty breathlessness services) included six publications: four systematic reviews[15-18] and two guidelines.[1,19]

The AHRQ systematic review on the treatment of dyspnea (questions 4-5) included 48 RCTs and two retrospective cohort studies.[11,12] Twenty-nine RCTs (2,423 patients) addressed the comparative benefits of nonpharmacologic interventions[20-48]; 17 RCTs and 1 retrospective cohort study (1,224 patients) addressed the comparative benefits of pharmacologic interventions[49-66]; and two RCTs (287 patients) addressed the comparative benefits of nonpharmacologic, pharmacologic, and multimodal interventions.[67,68] Strength of evidence ranged from insufficient to moderate, and was low for many of the interventions.

RECOMMENDATIONS

Clinical Question 1: How Should Dyspnea Be Assessed in Patients With Advanced Cancer?

Recommendation 1.1. Clinicians should perform systematic assessment of dyspnea at every inpatient and outpatient encounter in patients with advanced cancer using validated patient-reported outcome measures (good practice statement).

Recommendation 1.2. For patients who are unable to self-report, clinicians should use a validated observation measure. (good practice statement).

Recommendation 1.3. Whenever possible, patients with dyspnea should undergo a comprehensive evaluation for the severity, chronicity, potential causes, triggers, and associated symptoms, as well as emotional and functional impact (good practice statement).

Literature review and analysis. Systematic reviews have reported on several validated tools for the assessment of dyspnea in patients with cancer and other conditions.[15,17,18] Guidelines by the American Thoracic Society[1] and the European Society for Medical Oncology[19] discuss the importance of assessing and characterizing dyspnea.

Clinical interpretation. Because dyspnea is a subjective experience, patient-reported outcomes represent the gold standard for its assessment.[1] Dyspnea should be distinguished from hypoxemia. Patients with hypoxemia may not always be dyspneic and patients with dyspnea are often not hypoxemic.[69] Likewise, people with tachypnea may not feel breathless, and people with breathlessness may not have tachypnea.[69]

Commonly used patient-reported outcome measures for screening of dyspnea include the 0-10 Numeric Rating Scale, 0-10 modified Borg Scale, and the vertical 0-100 mm Visual Analog Scale, in which a higher number indicates worse dyspnea (Data Supplement).[70-72] The anchors for these scales can be selected to capture dyspnea intensity, unpleasantness, or distress.[73] These unidimensional outcomes have been validated in both clinical and research settings, are quick to administer (seconds to minutes), and relatively easy to understand and interpret for patients and clinicians. Patients may already be familiar with the Edmonton Symptom Assessment System, a multisymptom battery that uses the Numeric Rating Scale to measure 10 common symptoms including dyspnea (Data Supplement).[74,75]

In addition to the above scales, the modified Medical Research Council Breathlessness Scale may be added to assess dyspnea severity in relation to daily activity.[76] A personalized dyspnea goal "At what level would you feel comfortable?" may also be assessed to set individualized targets for dyspnea interventions.[77,78]

Patients who are delirious, comatose, near death, or intubated may not be able to report symptoms.[79] The Respiratory Distress Observation Scale has been validated across diagnoses and settings of care (Data Supplement).[80-84] It consists of eight variables, including heart rate, respiratory rate, restlessness or nonpurposeful movements, paradoxical breathing, accessory muscle use, grunting at end-expiration, nasal flaring, and look of fear. Other proxy rating measures such as the Integrated Palliative Care Outcome Scale may also be considered.[85]

Patients with episodic dyspnea should be asked about common triggers, such as activities (eg, walking, climbing stairs, running, bathing, and dressing), positions, weather, pollens, and emotional distress.[86] Symptoms associated with dyspnea may include, but are not limited to, depression, anxiety, fatigue, wheezing, and cough. Assessment of functional impact may include questions related to activities of daily living and performance status. Structured exercise tests including 6-minute walk test and shuttle walk test may provide further documentation of functional impairment because of dyspnea.[87,88]

Objective tests such as vital signs, pulmonary function tests, and imaging are complementary but do not replace

patient-reported outcomes in patients who can self-report. However, they may have a role in identifying underlying causes of dyspnea (eg, bronchospasm and malignant pericardial effusion).

Clinical Question 2: What Underlying Conditions Cause or Contribute to Dyspnea and Warrant Specific Management?

Recommendation 2.1. Patients with potentially reversible, common etiologies of dyspnea such as pleural effusion, pneumonia, airway obstruction, anemia, asthma, chronic obstructive pulmonary disease (COPD) exacerbation, pulmonary embolism, or treatment-induced pneumonitis should be given goal-concordant treatment(s) consistent with their wishes, prognosis, and overall health status (good practice statement).

Recommendation 2.2. Patients with dyspnea because of underlying malignancy (eg, lymphangitic carcinomatosis, atelectasis because of large pulmonary mass, and malignant pleural effusion) may benefit from cancer-directed treatments if consistent with their wishes, prognosis, and overall health status (good practice statement).

Recommendation 2.3 Patients with underlying comorbidities such as COPD or heart failure should have the management of these conditions optimized (good practice statement).

Literature review and analysis. Included publications did not directly address the effect of managing underlying causes of dyspnea, but two included guidelines noted that management of these conditions is an important initial step in dyspnea management.[1,19]

Clinical interpretation. In patients with advanced cancer, dyspnea is often multifactorial in nature with a combination of acute and chronic causes. For instance, a patient with metastatic lung cancer may experience chronic dyspnea related to lung mass compressing on mediastinum, atelectasis, pleural effusion, cachexia, COPD, and anxiety, with acute worsening because of coronavirus disease 2019 infection. Acute causes of dyspnea such as pneumonia, pulmonary embolism, decompensated heart failure, severe anemia, and COPD exacerbations should be managed according to standard of care. Dyspnea related to malignant pleural effusion, pericardial effusion and tamponade, and ascites may improve significantly with drainage.[89] Bronchoscopic interventions may be effective in alleviating dyspnea because of malignant central airway obstruction.[90] A full discussion of underlying causes is beyond the scope of this guideline.

For select patients with advanced cancer, systemic therapy may result in tumor response, contributing to symptomatic improvement.[91] Some malignancies are highly sensitive to systemic therapies, such as small-cell lung cancer and selected non–small-cell lung cancer with certain targetable mutations. Radiation may be useful for localized obstructing lesions or hemoptysis. At the same time, cancer treatments may contribute to significant adverse effects and thus the risks and benefits should always be carefully balanced, particularly in patients with limited life expectancy.

Patients with advanced cancer often have multiple comorbidities, which can contribute to greater symptom burden. For example, more than 50% of patients with lung cancer have a diagnosis of COPD, and the presence of COPD is associated with worse survival.[92-94] Optimal treatment of comorbid diagnoses is essential to alleviating dyspnea. Management of these comorbidities is beyond the scope of this guideline. Readers are encouraged to refer to specific clinical practice guidelines for the management of these conditions.[95,96] Primary care clinicians and/or other specialists such as pulmonologists should be actively engaged in the optimization of these comorbidities if not already.

Clinical Question 3: What Is the Role of Palliative Care in the Management of Dyspnea?

Recommendation 3. Patients with advanced cancer and dyspnea should be referred to an interprofessional palliative care team where available (type: evidence based; evidence quality: intermediate; strength of recommendation: strong).

Literature review and analysis. A 2019 systematic review and meta-analysis evaluated holistic services for patients with advanced disease and chronic breathlessness.[16] Holistic breathlessness services were defined as services in which patients were enrolled because of their breathlessness and that drew on skills from multiple disciplines to provide nonpharmacologic and pharmacologic interventions as well as self-management. The 18 specific breathlessness services that were included were all outside the United States, and a majority cared for patients with advanced cancer. The results suggested that holistic breathlessness services may reduce distress because of dyspnea.

Clinical interpretation. Patients with advanced cancer and dyspnea have a limited prognosis, multiple associated symptoms, and poor performance status.[8] In addition, they often experience psychosocial distress, spiritual and existential concerns, and caregiver needs that should be addressed longitudinally.[97] RCTs support that involvement of an interdisciplinary specialist palliative care team can help to improve dyspnea, self-efficacy, and overall quality of life.[28,98] Timely integration of specialist palliative care and oncologic care has been found to improve overall quality of life and symptom burden.[99-101] Consistent with the ASCO palliative care guideline,[102] this panel supports timely referral to palliative care, ideally starting in the outpatient setting. Systematic screening for dyspnea may facilitate automatic referral.[101,103,104]

Given the multifactorial nature of dyspnea and its multidimensional impact, multimodal interventions delivered by interprofessional teams can be beneficial. The interprofessional palliative care team typically includes advanced

practice nurses, nurses, physicians, social workers, chaplains, and pharmacists. Less often, other professionals such as physical therapists and mental health professionals may be part of the team. The palliative care team can improve dyspnea and other patient outcomes by monitoring symptoms longitudinally; educating patients and informal (family) caregivers about management strategies; implementing an array of nonpharmacologic and pharmacologic interventions; providing emotional, spiritual, and caregiver support; facilitating illness understanding, complex decision making, and advance care planning; and coordinating care with other disciplines.[105]

A breathlessness intervention service is a specialty dyspnea clinic typically comprised of representatives from palliative care, pulmonary medicine, physical and occupational therapy, and other professions. To date, several clinical trials involving cancer and noncancer patients reported that these clinics are associated with improved perceived self-efficacy for dyspnea.[28,98] These clinics often offer an array of nonpharmacologic and pharmacologic measures. Compared to palliative care services, they are more specialized in scope but are not as widely available.[106]

Clinical Question 4: What Nonpharmacologic Interventions Provide Palliation of Dyspnea?

Recommendation 4.1. Airflow interventions such as directing a fan at the cheek (trigeminal nerve distribution) should be offered (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 4.2. Standard supplemental oxygen should be available for patients with hypoxemia who are experiencing dyspnea (ie, $SpO_2 \leq 90\%$ on room air) (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 4.3. Supplemental oxygen is not recommended when $SpO_2 > 90\%$ (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 4.4. A time-limited therapeutic trial of high-flow nasal cannula oxygen therapy, if available, may be offered to patients who have significant dyspnea and hypoxemia despite standard supplemental oxygen (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Recommendation 4.5. A time-limited therapeutic trial of noninvasive ventilation, if available, may be offered to patients who have significant dyspnea despite standard measures and do not have contraindications (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Recommendation 4.6. Other nonpharmacologic measures such as breathing techniques, posture, relaxation, distraction, meditation, self-management, physical therapy, and music therapy may be offered (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 4.7. Acupressure or reflexology, if available, may be offered (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 4.8. Evidence remains insufficient for a recommendation for or against pulmonary rehabilitation in patients with advanced cancer and dyspnea.

Literature review and analysis. Twenty-nine RCTs that met inclusion criteria addressed nonpharmacologic interventions for dyspnea.[20-48] Based on three RCTs and 115 patients,[32,43,46] airflow interventions such as fans improved breathlessness compared with usual care or sham control, with moderate strength of evidence. Interventions that were associated with improvements in breathlessness with low strength of evidence were bilevel ventilation (compared with standard supplemental oxygen, one RCT[39]), acupressure or reflexology (*v* sham or usual care, two RCTs[27,47]), and multicomponent interventions that combined behavioral or psychoeducational interventions, activity or rehabilitation, and integrative medicine interventions (*v* usual care, two RCTs[28,48]).

With respect to anxiety, exercise capacity, and health-related quality of life (other key outcomes in the AHRQ review[11,12]), the only intervention associated with improvement was activity or rehabilitation, which improved exercise capacity with low strength of evidence (three RCTs, 72 patients[29,31,44]).

Clinical interpretation. Movement of air over the face may stimulate the trigeminal nerve and modulate the sensation of dyspnea. Randomized trials and systematic reviews report that fan or airflow therapy is associated with clinically significant and rapid alleviation of dyspnea.[107-109] A hand-held, battery-operated fan is portable, inexpensive, and can be used at any time.[110] A tabletop fan directed at the face may suffice if the patient cannot hold the device. In addition, medical air delivered by nasal cannula was also found to be beneficial.[111] Understandably, masking of patients is not possible for fan-based interventions (and other nonpharmacologic interventions), which could contribute to ascertainment bias. Nevertheless, given the favorable benefit-risk ratio for fan therapy, it represents the first-line, nonpharmacologic measure for palliation of dyspnea. The duration of benefit needs to be further examined.

Standard supplemental oxygen typically involves a nasal cannula delivering 2-6 L/min of oxygen. In patients with hypoxemia, standard supplemental oxygen is recommended. Although humidification has been suggested to reduce dry nose and nosebleed, a systematic review that included 8,876 patients from 27 randomized trials reported that nonhumified oxygen was associated with less bacterial contamination and lower rates of respiratory infections and no more increase in dry nose and nosebleed compared with humidified oxygen.[112] Some patients only experience

hypoxemia with exertion and may only require as needed supplemental oxygen before or during activity, whereas those with hypoxemia at rest may benefit from continuous use. It should be noted that correction of hypoxemia may not reverse dyspnea, especially if hypoxemia is not the only contributor. In the United States, insurance may not cover standard supplemental oxygen when the SpO_2 is > 88%.

Oxygen saturation is expected to drop in the last hours before death. It is important to carefully balance the risks and benefits of supplemental oxygen. When there are no signs of respiratory distress, oxygen, if in use, may be withdrawn. Oxygen saturation monitoring may not be useful in this setting, and clinicians should discuss risks and benefits of treatment and provide recommendations based on the patient's stated goals of care.[113]

Although clinical trials reported no benefit of standard supplemental oxygen compared with medical air for dyspnea in the absence of hypoxemia, some patients in the control group reported dyspnea relief with medical air, which may be related to airflow.[20,22,40,114,115] Although we do not recommend routine use of standard supplemental oxygen in nonhypoxemic patients with dyspnea, a time-limited trial of low-flow oxygen or air may still be reasonable for select patients, given the low risk of this intervention; however, fan therapy should be considered first. See Table 2 for a suggested approach to initiating standard supplemental oxygen.

High-flow nasal cannula oxygen therapy can deliver up to 80 L/min of heated and humidified oxygen. In addition to oxygenation, high-flow nasal cannula oxygen therapy may alleviate dyspnea by multiple mechanisms, such as improving ventilation with nasopharyngeal washout (ie, better clearing of upper airway deadspace), stimulating the trigeminal nerves, augmenting positive airway pressure, reducing work of breathing, and conditioning of inhaled gas (ie, heated and humidified).[116,117] A small RCT provided preliminary evidence to support the benefit of this modality in patients with cancer.[30]

Clinicians should weigh the risks and benefits of high-flow nasal cannula oxygen therapy, considering underlying pathophysiology, prognosis, patient preference, logistics, and costs. Goals of treatment should always be discussed before initiation of high-flow nasal cannula oxygen therapy. This intervention may necessitate continued hospitalization if the high flows cannot be achieved at home depending on local availability. Other interventions should be administered if high-flow nasal cannula oxygen therapy is more burdensome than beneficial after a time-limited therapeutic trial (typically < 1 hour).

Respiratory therapists are often involved in the day-to-day delivery of high-flow oxygen, selecting the most appropriate interface and titrating device settings. Setting of the device is an important issue to consider since it may affect its tolerance. It is important to work with the patient to choose the proper nasal cannula (small, medium, and large), set temperature as tolerated (generally between 34°C and 37°C), and the flow rate (usually start at 45-50 L/min but may decrease down to 20 L/min or increase gradually up to 60 L/min, depending on the level of patient's comfort). Communication among the oncology, palliative care, pulmonary medicine, and/or respiratory care teams is essential to ensure interventions are aligned with the goals of treatment.

Noninvasive ventilation can improve oxygenation and ventilation by providing positive end-expiratory pressure and augmenting respiratory muscles. Patients with hypercapnic respiratory failure are more likely to benefit from noninvasive ventilation.[39] The potential benefits should be weighed against potential adverse events, such as skin breakdown, muffled communication, claustrophobia, and inability to eat. Contraindications to noninvasive ventilation include facial trauma, decreased level of consciousness, severe vomiting, inability to clear secretions, and severe claustrophobia.

Clinicians should weigh the risks and benefits of noninvasive ventilation, taking into account underlying pathophysiology, prognosis, patient preference, logistics, and costs. Goals of treatment should always be discussed before initiation of noninvasive ventilation.[118,119] Other interventions should be administered if noninvasive ventilation is more burdensome than beneficial after a time-limited therapeutic trial (typically < 1 hour). Clinicians should be cautious about using noninvasive ventilation in the last days of life because it may be more burdensome than beneficial.[119]

Respiratory therapists are often involved in the day-to-day delivery of noninvasive ventilation, selecting the most appropriate interface, and titrating device settings. When initiating noninvasive ventilation, consider starting with low inspiratory pressure (ie, 8-10 cmH_2O) and then gradually increase as tolerated. Expiratory pressure should never be above 6-8 cmH_2O unless indicated (eg, cardiogenic

TABLE 2. Supplemental Oxygen Use

Dyspnea or Respiratory Distress	Oxygen Saturation	Oxygen Indicated	Other Interventions Indicated
Present	< 90%	Yes, start low	Yes, to treat underlying cause of hypoxemia
Present	≥ 90%	No; however, airflow alone can be beneficial	Yes, to treat underlying cause of dyspnea
Absent	< 90%	Yes, for oxygenation purpose, unless last days of life	Yes, to treat underlying cause of hypoxemia
Absent	≥ 90%	No, consider withdrawal if in use	No

pulmonary edema). Choose the more appropriate size and type of interfaces (ie, nasal, oronasal, total face, or mouthpiece) based on patient tolerance and set the initial flow rate (or ramp), according to the patient's need. Similar to high-flow oxygen, collaboration among oncology, palliative care, pulmonary medicine, and/or respiratory care teams is essential to ensure care is aligned with the goals of treatment.

The evidence to support breathing techniques, posture, relaxation or meditation, assistive devices, and education or self-management is mixed and mostly derived from studies in patients with COPD instead of cancer.[120] However, given these self-administered strategies are relatively simple, inexpensive, low risk, and have some preliminary supportive evidence, patients with dyspnea may be counseled on adopting these interventions.

Breathing techniques include pursed lip, abdominal, and timed breathing. In an unblinded randomized clinical trial, a single 20-minute session of mindful breathing was found to improve dyspnea in patients with cancer.[121] A Cochrane systematic review reported that exercise capacity improved with breathing exercises; however, their effects on dyspnea were inconsistent.[120] Various postures such as relaxed sitting, high-side lying, and standing against a wall have been proposed to improve breathing dynamics.[122]

Education and self-management programs typically involve educating patients about the nature of dyspnea, developing coping strategies, learning about breathing techniques and postures, providing emotional support, and setting management goals.[36,123] Many programs promote optimizing physical function through exercise training[124] and activity pacing; others incorporate mindfulness techniques such as guided imagery and meditation. These programs are often led by nurses and/or physical or occupational or respiratory therapists. Although the evidence is mixed regarding these programs, the panel considered these minimal-risk strategies to have potential benefits and a trial may be considered.

The level of evidence to support acupressure and reflexology is low, and the dose and duration for these interventions have not been standardized. These complementary interventions are practitioner-dependent. If considered, referral to a licensed therapist is warranted.

Pulmonary rehabilitation is well established in patients with underlying cardiopulmonary disorders and should be offered for individuals with these conditions. This intervention typically involves multiple weeks of structured exercise sessions conducted under the supervision of physical and/or occupational therapists; other disciplines are sometimes involved and patients are often taught some self-management techniques. In patients with COPD, pulmonary rehabilitation has been found to improve dyspnea, fatigue, and health-related quality of life.[125] Patients with advanced cancer often have a short survival and it is unclear if they would derive the same benefit.

Clinical Question 5: What Pharmacologic Interventions Provide Palliation of Dyspnea?

Pharmacologic measures should be considered in patients with advanced cancer and acute and/or chronic dyspnea when treatment of underlying conditions and nonpharmacologic therapies do not yield patient relief (Recommendations 4.1-4.8). Patients presenting with acute severe dyspnea may not have enough time for a stepwise introduction of interventions, and a concurrent approach with both pharmacologic and nonpharmacologic strategies is warranted.

Recommendation 5.1. Systemic opioids should be offered to patients with dyspnea when nonpharmacologic interventions are insufficient to provide dyspnea relief (type: evidence-based; evidence quality: low; strength of recommendation: moderate).

Recommendation 5.2. Short-acting benzodiazepines may be offered to patients who experience dyspnea-related anxiety and who continue to experience dyspnea despite opioids and other nonpharmacologic measures (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 5.3. Systemic corticosteroids may be offered to select patients with airway obstruction or when inflammation is likely a key contributor of dyspnea (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 5.4. Bronchodilators should be used for palliation of dyspnea when patients have established obstructive pulmonary disorders or evidence of bronchospasm (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 5.5. Evidence remains insufficient for a recommendation for or against the use of antidepressants, neuroleptics, or inhaled furosemide for dyspnea.

Recommendation 5.6. Continuous palliative sedation should be offered to patients with dyspnea that is refractory to all standard treatment options and all applicable palliative options, and who have an expected life expectancy of days (type: informal consensus; evidence quality: low; strength of recommendation: moderate).

Literature review and analysis. Of the 17 RCTs[49-65] assessing pharmacologic interventions included in the AHRQ systematic review,[11] six[51,53,57,59,60,64] reported on opioids versus placebo with respect to breathlessness. Sample size in these studies ranged from 20 to 40, with a total of 107 patients evaluated. With moderate strength of evidence, opioids were no more effective than placebo at improving breathlessness. Similarly, based on two RCTs[55,63] in 311 patients and low strength of evidence, anxiolytics were no more effective than placebo with respect to breathlessness. Only a single, small RCT

addressed corticosteroids, and evidence was deemed insufficient for a conclusion.[58]

Clinical interpretation. Although the systematic review focusing only on patients with cancer did not identify a benefit for opioids, there are significant limitations to the few included clinical trials, including small sample sizes, short study duration, and variability in outcome measures. Several systematic reviews concluded that opioids have a clear pharmacologic effect when the greater literature on opioids, including other patient populations such as COPD, is taken into consideration; thus, we conclude that opioids are likely to be effective.[126-128] Despite the paucity of high-quality evidence specifically in patients with advanced cancer, the risk of inaction is greater than a recommendation to support opioid use because dyspnea is extremely distressing and many patients continue to experience dyspnea despite optimal nonpharmacologic therapies. Thus, the panel endorses a time trial of opioids for dyspnea.

There is insufficient evidence to inform the choice of opioid. However, the choice of systemic opioid, route (eg, intravenous, subcutaneous, oral, rectal, and transmucosal), and formulation should be guided by what opioids patients are already taking, comorbidities (eg, renal insufficiency), risk profile (eg, nonmedical opioid use), its effect on dyspnea and adverse effects, clinical setting (inpatient *v* outpatient), and logistical considerations (eg, financial). More RCTs on dyspnea have examined morphine and fentanyl. No studies have definitively confirmed the effect of hydromorphone, oxycodone, methadone, or hydrocodone on dyspnea. For patients in the last days of life who have difficulty swallowing, opioids can be administered via the intravenous route, subcutaneous route, transmucosal route, or rectal route (eg, suppositories). Concentrated morphine sulfate elixir may also be placed in the buccal space.[129] Despite mixed evidence, nebulized opioids may also be considered in selected patients in whom systemic opioids are not feasible.[126,130]

Insufficient evidence on the optimal dosing regimen of opioids for the management of dyspnea exists. The general principles are to start low and titrate over time to desired effect. Optimal dosing of opioids should be informed by pharmacokinetics and the clinical context.

Opioids may be considered in three clinical situations. Given the paucity of data, the doses are for general references only.[131]

- For hospitalized patients with acute severe dyspnea, parenteral (subcutaneous or intravenous) opioids should be provided. For patients who are opioid-naive, parenteral morphine 2 mg or equivalent may be used on an as-needed basis. For patients who are opioid-tolerant and continue to experience dyspnea, a rescue opioid dose equivalent to 10%-25% of morphine-equivalent daily dose (MEDD) has been used in clinical trials.
- For ambulatory patients with activity-induced dyspnea, short-acting oral or rapid-acting transmucosal opioids may be considered before selected activities for prophylaxis. For patients who are opioid-naive, single doses of MEDD of 5-10 mg orally may be used. For patients who are opioid-tolerant who continue to experience dyspnea, a rescue opioid dose equivalent to 15%-45% of MEDD may be appropriate before activities. The dose of opioid should be timed in relation to the pharmacokinetic profile of the opioid (eg, 30 minutes before activity for oral immediate release opioids).
- For patients with chronic breathlessness, scheduled short-acting opioids or long-acting opioids may be offered. For patients who are opioid-naive, the starting dose is typically morphine sulfate 10-30 mg orally per day.[132] For patients who are opioid-tolerant who continue to experience dyspnea, an increase in their basal opioid dose by 30% may be appropriate. The upper limit of opioid dose is based on adverse effects (eg, neurotoxicities).

The duration of opioid use should be based on the risk-benefit ratio, with the use of opioids regularly evaluated to ensure the ratio remains favorable. When first using opioids for dyspnea, a time trial should be considered with close monitoring to evaluate derived benefits and/or adverse effects. The opioid doses may be titrated up or down every 3-4 days in the outpatient setting or daily in the inpatient setting to optimize patient outcomes.

Opioids are associated with many known adverse effects, such as constipation, nausea, drowsiness, pruritus, bronchospasm, and nonmedical opioid use.[133] Nausea and drowsiness often abate after a few days; however, constipation never abates. Clinicians should educate patients and informal caregivers regarding the risks and benefits of opioid therapy and the safe use, storage, and disposal of controlled substances (see ASCO chronic pain guideline[134]) as well as educated on appropriate preventative strategies, such as the use of stimulant laxatives for constipation prophylaxis. Some patients and clinicians are concerned about the risk of respiratory depression with opioid use. In a meta-analysis that included 63 articles and more than 1,000 patients, the investigators found no evidence of significant or clinically relevant respiratory adverse effects when opioids are prescribed and used properly for chronic dyspnea.[135]

The literature on inhaled or nebulized opioids is limited and mixed in both the oncology and nononcology settings. Oral and parenteral routes are preferred over the inhaled route because of reliable drug delivery and literature support for clinical efficacy. However, these routes may not be possible or feasible in some patients and the inhaled route may be considered in select patients. In one before-after trial, fentanyl 25 mcg in 2 cm^3 normal saline by nebulizer was

reported useful among patients cared for in an inpatient palliative care unit.[136]

In general, the use of benzodiazepines in patients with advanced cancer should be minimized because of their sedative effect, and patients with dyspnea are often already at high risk of delirium.[137] Moreover, concurrent use of benzodiazepines and opioids or other psychotropic medications may further increase the adverse effects, including the risk of respiratory depression.[138,139] Therefore, benzodiazepines should not be offered as first-line treatment of dyspnea. Although benzodiazepines have not been demonstrated to be better than placebo in the systematic reviews, the panel recognizes that some patients with severe anxiety or distress related to dyspnea despite other interventions may benefit from a trial of benzodiazepines, given the risk of inaction is higher. In such situations, short-acting benzodiazepines such as midazolam 2-5 mg q4h have been used in clinical trials.[61,62]

To date, only one small pilot study has examined the effect of dexamethasone on dyspnea as the primary outcome in patients with cancer. Dexamethasone 8 mg PO twice daily was associated with an improvement of dyspnea within the first 4 days compared with placebo.[58] A large confirmatory trial is ongoing (ClinicalTrials.gov identifier: NCT03367156). Several randomized trials have examined breathlessness as a secondary outcome. In one study, 84 patients with cancer-related fatigue received either 4 mg dexamethasone twice daily for 14 days or placebo. There was a trend favoring dexamethasone for breathlessness (mean -2.16 *v* -0.89, $P = .06$).[140] Another randomized trial enrolled 298 patients undergoing radiation for bone metastases. Dyspnea significantly improved with dexamethasone 8 mg daily for 5 days (mean -0.3 *v* 2.8, $P = .02$). Dexamethasone also improved radiation-induced pain flare.[141] A few small case reports or series reported that corticosteroids may be particularly helpful for central airway obstruction, lymphangitic carcinomatosis, and superior vena cava syndrome.[142,143] Nevertheless, no randomized trials have been conducted to specifically examine these conditions.

Short-term systemic corticosteroids (eg, dexamethasone 8-16 mg/d for 1 week) may be considered in select patients, with close monitoring to assess if they experience any benefits or adverse effects. A small prospective observational study examined predictors of response to corticosteroids. Patients with high baseline dyspnea scores ($\geq$ 7/10), better prognosis (Palliative Prognostic Index $<$ 6), and no liver or ascites involvement were more likely to derive a benefit.[144] Corticosteroids are associated with significant short-term (eg, hyperglycemia, hiccups, facial flushing, dyspepsia, and insomnia) and long-term (eg, hypertension, edema, muscle wasting, and immunosuppression) adverse effects. They may also affect the efficacy of immunotherapy and radiotherapy.[145,146]

Patients who were prescribed bronchodilators for COPD and asthma should continue with their use (see Recommendation 2.3). However, bronchodilators should not be used in patients without evidence of bronchospasm. If used, bronchodilators should not exceed the maximum daily dose. Supratherapeutic doses may reduce the bronchodilator effects while increasing the cardiovascular adverse effects.[147] A detailed discussion of bronchodilators is beyond the scope of this guideline and discussed elsewhere.[96]

Several clinical trials have examined the effect of antidepressants on dyspnea, including sertraline, nortriptyline, paroxetine, and protriptyline, mostly in patients with COPD.[148-152] Some studies only enrolled patients with depression, whereas others were less restrictive. A majority of randomized trials did not demonstrate superiority of antidepressants over placebo and only a few of these randomized trials included patients with cancer.

Randomized trials have examined the effects of prochlorperazine, promethazine, and chlorpromazine on dyspnea with inconsistent findings.[153-155] Neuroleptics may be associated with side effects and should not be used outside of a clinical trial setting.

Two small randomized trials of inhaled furosemide in patients with cancer did not identify a benefit.[156,157] Adverse effects of inhaled furosemide may include pharyngeal irritation, cough, and polyuria.

For hospitalized patients with refractory dyspnea despite all standard measures, continuous palliative sedation may be considered in select cases. The goal of palliative sedation is to alleviate suffering. Some patients may be reassured that this option is available if their dyspnea became extremely severe, even if they may never have to use it. Two studies found that palliative sedation did not shorten survival.[158,159]

A detailed discussion of palliative sedation is beyond the scope of this guideline and discussed elsewhere.[160] Specialist palliative care teams should be involved in facilitating the complex communication and medication administration in this setting. The most common medication for palliative sedation is midazolam infusion to provide continuous deep sedation. Before initiation of palliative sedation, the healthcare team should have an extensive discussion with patients (if able to retain decision-making capacity) and caregivers about the risks and benefits. Ethics consultation may also be helpful, if available.

DISCUSSION

Dyspnea is a challenging symptom to treat and currently, the US Food and Drug Administration has not approved any therapies for dyspnea.[161] A paucity of high-quality evidence exists to inform clinical decision making (see section on Limitations of the Research and Future Research). This guideline aims to provide state-of-the-science recommendations on the management of dyspnea in the advanced cancer setting. Although the principles of management are the same, specific recommendations may vary in different

settings. To that end, we have included several flow diagrams to highlight key differences (Figs 1-3).

Figure 1 summarizes the management of chronic dyspnea, which is predominantly in the ambulatory setting. Systematic screening for dyspnea should be conducted at every visit, which would facilitate early detection of dyspnea and timely stepwise intervention. In patients who continue to experience dyspnea despite treatment of underlying causes, referral to specialist palliative care is warranted. The interprofessional palliative care team not only works with the patient to treat dyspnea and associated symptoms but also facilitates goals-of-care discussions. Nonpharmacologic therapies should be recommended before a trial of pharmacologic therapies such as opioids. In the ambulatory setting, oral opioids are used for treatment of everyday dyspnea and/or prophylaxis of exertional dyspnea.

Figure 2 outlines the management of acute dyspnea, which is mostly in the inpatient setting. Systematic daily screening is recommended. Given the acute and severe nature of dyspnea, interventions should be introduced concurrently instead of in a stepwise manner. For patients who remain hypoxemic despite standard supplemental oxygen, high-flow oxygen and noninvasive ventilation may be considered. Home versions of these devices are available at discharge if required. In contrast to the ambulatory setting, hospitalized patients may require parenteral opioids for treatment of acute episodes of dyspnea via continuous infusion and/or boluses.

Figure 3 outlines management of terminal dyspnea involving patients in the last days of life. In this setting, patients are often delirious and may not be able to communicate their concerns and make decisions. Some patients may be intubated in the critical care unit. Involvement of the surrogate decision maker in patients who have lost their decision-making capacity is critical. Although some patients may still benefit from treatment of underlying causes, the risks of treatment often outweigh the benefits in this setting and further cancer treatments are no longer recommended in these patients. Similarly, many nonpharmacologic interventions such as self-management may not be feasible. Given the limited time, rapid titration of pharmacologic therapies is often necessary to maximize comfort. In patients with refractory dyspnea and severe distress, palliative sedation may be considered as a last resort.

PATIENT AND CLINICIAN COMMUNICATION

For general recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[162]

Because dyspnea in the advanced cancer setting, by nature, involves patients with greater distress, poorer function, and worse survival, many of the decisions regarding investigations and treatment need to be discussed carefully. The management of dyspnea in patients with months of life expectancy can be very different from patients with days of life expectancy. As discussed above, it is important to set realistic expectations for what can be achieved, setting a time to revisit the decision after a short trial, and ensure the management approach is concordant with the goals and wishes expressed by patients and caregivers.

Many of the nonpharmacologic approaches such as airflow therapy and self-management require patients to be actively involved in the delivery of the interventions. Patients need to understand the principles and concepts and feel comfortable applying the techniques, such as activity pacing or breathing training, and use of fans. A randomized trial compared three breathing technique training sessions to a single session and reported improvement in both groups with no difference in worst dyspnea, suggesting that a single session may be adequate.[163] Initiation of high-flow oxygen and noninvasive ventilation warrants training the informal caregiver along with the patient.

For pharmacologic therapies, the benefit-to-risk ratio is more variable and needs to be explored with patients and their caregivers. A time-limited trial may be worthwhile. For example, although opioids confer some benefits for dyspnea, they are also associated with potential adverse effects. Patients should be counseled on proper and safe opioid use and storage. Some patients may be fearful about opioids, requiring significant counseling. Others may have significant risk factors for nonmedical opioid use, and the benefit-to-risk ratio will need to be monitored closely.

Informal caregivers play a critical role in supporting the patients' physical needs, providing emotional support, aiding with decision making, and assisting with care planning.[164] In patients who can no longer communicate (eg, intubated and delirious patients), they serve as surrogate decision makers. Informal caregivers of patients with advanced cancer and dyspnea often have their own information needs (eg, coping and prognosis) and may experience distress related to increased caregiver burden, exhaustion, anxiety, and uncertainty as the patients' functional status declines.[165,166] Several studies support the role of palliative care, breathlessness intervention service, and psychoeducational interventions for informal caregivers; however, further research is needed.[28,98]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic

minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality compared with other patients.[167-169] Many patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and clinicians should strive to deliver the highest level of cancer care to these vulnerable populations. An updated ASCO policy statement on cancer disparities and health equity was published in August 2020.[170] The statement focuses on improving equitable access to care, improving clinical research, addressing structural barriers, and increasing awareness.

Few studies have addressed disparities in dyspnea management among patients with cancer, but a 2016 evaluation of patients with lung or colorectal cancer enrolled in the Cancer Care Outcomes Research and Surveillance (CanCORS) study considered the impact of financial strain on symptom burden.[171] Among patients with lung cancer, patients with fewer financial reserves reported worse dyspnea measures even after adjustment for age, sex, race or ethnicity, household income, education, health insurance, cancer stage, and comorbidity. The researchers hypothesize that this could be because of worsening disease burden, inability to access high-quality supportive care, or difficulty obtaining medications.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

Dyspnea is prevalent in advanced cancer and cardiopulmonary conditions, which covary particularly among patients who used tobacco products. Among patients with lung cancer, more than 50% were also diagnosed with COPD.[92-94] Cachexia is also highly prevalent in patients with advanced cancer and may contribute to dyspnea secondary to atrophy of respiratory muscles and cardiac muscular dysfunction.[172,173] Last days organ failure, particularly liver and renal, will affect the efficacy of the recommended pharmacologic interventions. Involvement of the interprofessional team and appropriate subspecialties may be necessary to optimize management of these comorbid conditions. The clinical implications of the recommendations in the guideline gave consideration to the implication of MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[174,175] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[176,177]

Discussion of cost can be an important part of shared decision making.[178] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[178]

Many nonpharmacologic therapies such as fan and self-management strategies are associated with no or very limited cost. Others such as reflexology may involve greater expenses over multiple sessions. Prescription of opioids for dyspnea is off label. Many of the medications for dyspnea, such as morphine and dexamethasone, are available as generic forms and are relatively inexpensive. Rapid-onset fentanyl and some combination bronchodilators can be much more expensive.

Patient out-of-pocket costs may vary depending on insurance coverage. Supplemental oxygen therapy in the outpatient setting may pose a cost for the patient if the insurance coverage is denied for an $SpO_2 > 88\%$. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan.

Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[178]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from September 1 to September 15, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation with six written comments received. Five of the six reviewers agreed or agreed with suggested modifications to the recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before Center for Peace and Global Citizenship (CPGC) review and approval.

The draft was submitted to two external reviewers with content expertise. Review comments were reviewed by the Expert Panel and integrated into the final manuscript before approval by the CPGC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

LIMITATIONS OF THE RESEARCH AND FUTURE RESEARCH

As noted above, the literature on dyspnea has major limitations. We will focus our discussion here on RCTs that are essential to inform treatment recommendations. Few clinical trials have focused on cancer-related dyspnea, partly related to the lack of funding and investigators. This is not surprising, given that patients with advanced cancer and dyspnea often have a poor performance status, significant distress, and short survival, making them less likely to enroll and stay on clinical trials. For example, attrition from clinical trials is higher among advanced cancer patients with dyspnea at baseline.[179] This also explains why the few clinical trials in this setting are often preliminary in nature with a small sample size (often < 30 patients), which could contribute to both false-negative and false-positive findings. Other studies have tried to address the sample size concern with a mixed population of cancer and noncancer patients, which could complicate interpretability and generalizability.

Methodologic challenges related to dyspnea as a subjective outcome should also be highlighted. There is increased understanding that, similar to pain, dyspnea is not a single entity but one with many subtypes that may require different treatment approaches. Specifically, dyspnea can be classified as dyspnea at rest, episodic dyspnea, and everyday dyspnea, and also based on chronicity (acute *v* chronic). Currently, many studies on everyday dyspnea have not accounted for activity levels when assessing dyspnea. Effective interventions for dyspnea may be declared negative if they improved function or dyspnea-related distress but not dyspnea intensity if patients tried to do as much as they could tolerate. Response to an intervention may be determined by diagnosis (eg, cancer *v* noncancer) and pathophysiology (obstructive lung disease, restrictive lung disease, mixed, and nonpulmonary). For instance, bronchodilators have been found to be efficacious in patients with COPD but their role in patients with cancer remains unclear. Furthermore, the applicability of an intervention may be limited by settings (inpatient, outpatient, and community) and disease trajectory (months *v* weeks or days). Currently, many studies have mixed or ill-defined patient populations, which may not allow them to detect an adequate signal. Furthermore, different investigators have chosen different patient-reported outcome measures to assess dyspnea with different time anchors and variable degrees of validation.[17] The concept of minimal clinically important difference has its own limitations. It is not often available for an instrument and when available, may not be applicable to a specific patient population. Response shift may further complicate interpretation. In some studies, dyspnea is only an exploratory outcome rather than primary end point.

Choice of study intervention and control could also have a major impact on the outcome. There is inadequate understanding of the pathophysiology of dyspnea to develop novel interventions. There are few dose-finding studies, and underdosing of an intervention may contribute to negative findings. Pharmacologic trials may include placebo control for proper blinding, but placebo effect may be of benefit itself, and interventions that showed within-group improvement but no between-group difference against placebo may be concluded as ineffective. Nonpharmacologic studies typically are not blinded, which may represent a source of ascertainment bias.

Taken together, the few available studies, heterogeneous patient populations, small sample size, choice of

interventions and controls, and limitations with study outcomes explain why there remain many unanswered questions and few established interventions for dyspnea. Below is a list of contemporary research questions:

- What is the natural history and pathophysiology of dyspnea?
- How is dyspnea experienced in patients with cancer compared with other populations?
- What is the optimal combination of multimodal therapy?
- For what type of dyspnea (chronic *v* episodic) is an intervention most efficacious?
- What is the most appropriate study outcome? How to account for dyspnea and physical function at the same time?
- How to define dyspnea response?
- Who are the patients most likely to benefit from a specific intervention?
- What are the short- and long-term adverse effects of treatment?
- What are the right medication, dose, dosing schedule, and timing for treatment administration?

Given the high prevalence of this symptom in patients with advanced cancer, its distressing nature, and functional impact, more high-quality research is needed to develop novel interventions to support patients and informal caregivers. Funding agencies need to prioritize dyspnea interventions to catalyze research in this area. Collaboration among investigators would allow sharing of expertise to optimize study designs, facilitate multicenter recruitment to increase sample size, and maximize generalizability and knowledge translation.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Management of Chronic Pain in Survivors of Adult Cancers[134] (https://ascopubs.org/doi/full/10.1200/JCO.2016.68.5206)
- Integration of Palliative Care into Standard Oncology Practice[102] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[162] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

AFFILIATIONS

[1]MD Anderson Cancer Center, Houston, TX
[2]American Society of Clinical Oncology, Alexandria, VA
[3]Memorial Sloan Kettering Cancer Center, New York, NY
[4]University of Wisconsin-Madison, Madison, WI
[5]Medical University of South Carolina, Charleston, SC
[6]University of Technology Sydney, Sydney, Australia
[7]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD
[8]Rutgers RWJ Cancer Institute of New Jersey, New Brunswick, NJ
[9]Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan
[10]IRCCS Azienda Ospedaliera University of Bologna, S. Orsola-Malpighi Hospital, Alma Mater University, Bologna, Italy
[11]VA Puget Sound Health Care System, Seattle, WA
[12]Massachusetts General Hospital Cancer Center, Boston, MA
[13]Patient/family representative, Brookline, MA
[14]Levine Cancer Institute, Charlotte, NC
[15]Wayne State University, Detroit, MI

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

EQUAL CONTRIBUTION

D.H. and M.L.C. were Expert Panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.03465.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The Expert Panel wishes to thank Drs Eduardo Bruera, DorAnne Donesky, Christine Miaskowski, Jamie Lesnock, and the Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this guideline. Arjun Gupta is supported by an American Society of Clinical Oncology (ASCO) Young Investigator Award.

REFERENCES

1. Parshall MB, Schwartzstein RM, Adams L, et al: An official American Thoracic Society statement: Update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 185:435-452, 2012
2. Solano JP, Gomes B, Higginson IJ: A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manage 31:58-69, 2006
3. Seow H, Barbera L, Sutradhar R, et al: Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. J Clin Oncol 29:1151-1158, 2011
4. Hui D, dos Santos R, Chisholm GB, et al: Symptom expression in the last seven days of life among cancer patients admitted to acute palliative care units. J Pain Symptom Manage 50:488-494, 2015
5. Campbell ML, Kiernan JM, Strandmark J, et al: Trajectory of dyspnea and respiratory distress among patients in the last month of life. J Palliat Med 21: 194-199, 2018
6. Currow DC, Smith J, Davidson PM, et al: Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study. J Pain Symptom Manage 39:680-690, 2010
7. Tishelman C, Petersson LM, Degner LF, et al: Symptom prevalence, intensity, and distress in patients with inoperable lung cancer in relation to time of death. J Clin Oncol 25:5381-5389, 2007
8. Reddy SK, Parsons HA, Elsayem A, et al: Characteristics and correlates of dyspnea in patients with advanced cancer. J Palliat Med 12:29-36, 2009
9. Cuervo Pinna MA, Mota Vargas R, Redondo Moralo MJ, et al: Dyspnea: A bad prognosis symptom at the end of life. Am J Hosp Palliat Care 26:89-97, 2009
10. Lovell N, Etkind SN, Bajwah S, et al: Control and context are central for people with advanced illness experiencing breathlessness: A systematic review and thematic synthesis. J Pain Symptom Manage 57:140-155.e2, 2019
11. Dy SM, Gupta A, Waldfogel JM, et al: Interventions for Breathlessness in Patients With Advanced Cancer. Comparative Effectiveness Review No. 232, AHRQ Publication No. 21-EHC024, PCORI Publication No. 2020-SR-01. Rockville, MD, Agency for Healthcare Research and Quality, 2020
12. Gupta A, Sedhom R, Sharma R, et al: Nonpharmacological interventions for managing breathlessness in patients with advanced cancer: A systematic review. JAMA Oncol 10.1001/jamaoncol.2020.5184 [epub ahead of print on November 19, 2020]
13. Guyatt GH, Alonso-Coello P, Schünemann HJ, et al: Guideline panels should seldom make good practice statements: Guidance from the GRADE Working Group. J Clin Epidemiol 80:3-7, 2016
14. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. J Am Med Inform Assoc 19:94-101, 2012
15. Bausewein C, Farquhar M, Booth S, et al: Measurement of breathlessness in advanced disease: A systematic review. Respir Med 101:399-410, 2007
16. Brighton LJ, Miller S, Farquhar M, et al: Holistic services for people with advanced disease and chronic breathlessness: A systematic review and meta-analysis. Thorax 74:270-281, 2019
17. Dorman S, Byrne A, Edwards A: Which measurement scales should we use to measure breathlessness in palliative care? A systematic review. Palliat Med 21: 177-191, 2007
18. Elliott-Button HL, Johnson MJ, Nwulu U, et al: Identification and assessment of breathlessness in clinical practice: A systematic review and narrative synthesis. J Pain Symptom Manage 59:724-733.e19, 2020
19. Hui D, Maddocks M, Johnson J, et al: Management of breathlessness in patients with cancer: ESMO clinical practice guidelines. ESMO Open 5:e001038, 2020
20. Booth S, Kelly MJ, Cox NP, et al: Does oxygen help dyspnea in patients with cancer? Am J Respir Crit Care Med 153:1515-1518, 1996
21. Bordeleau L, Szalai JP, Ennis M, et al: Quality of life in a randomized trial of group psychosocial support in metastatic breast cancer: Overall effects of the intervention and an exploration of missing data. J Clin Oncol 21:1944-1951, 2003
22. Bruera E, de Stoutz N, Velasco-Leiva A, et al: Effects of oxygen on dyspnoea in hypoxaemic terminal-cancer patients. Lancet 342:13-14, 1993
23. Bruera E, Sweeney C, Willey J, et al: A randomized controlled trial of supplemental oxygen versus air in cancer patients with dyspnea. Palliat Med 17:659-663, 2003
24. Chan CW, Richardson A, Richardson J: Managing symptoms in patients with advanced lung cancer during radiotherapy: Results of a psychoeducational randomized controlled trial. J Pain Symptom Manage 41:347-357, 2011
25. Corner J, Plant H, A'Hern R, et al: Non-pharmacological intervention for breathlessness in lung cancer. Palliat Med 10:299-305, 1996
26. Dhillon HM, Bell ML, van der Ploeg HP, et al: Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: A randomized controlled trial. Ann Oncol 28:1889-1897, 2017
27. Doğan N, Taşcı S: The effects of acupressure on quality of life and dyspnea in lung cancer: A randomized, controlled trial. Altern Ther Health Med 26:49-56, 2020
28. Farquhar MC, Prevost AT, McCrone P, et al: Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. BMC Med 12:194, 2014
29. Henke CC, Cabri J, Fricke L, et al: Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. Support Care Cancer 22: 95-101, 2014
30. Hui D, Morgado M, Chisholm G, et al: High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: A phase II randomized trial. J Pain Symptom Manage 46:463-473, 2013
31. Hwang CL, Yu CJ, Shih JY, et al: Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy. Support Care Cancer 20:3169-3177, 2012
32. Kako J, Morita T, Yamaguchi T, et al: Fan therapy is effective in relieving dyspnea in patients with terminally ill cancer: A parallel-arm, randomized controlled trial. J Pain Symptom Manage 56:493-500, 2018
33. Ligibel JA, Giobbie-Hurder A, Shockro L, et al: Randomized trial of a physical activity intervention in women with metastatic breast cancer. Cancer 122: 1169-1177, 2016
34. McMillan SC, Small BJ: Using the COPE intervention for family caregivers to improve symptoms of hospice homecare patients: A clinical trial. Oncol Nurs Forum 34:313-321, 2007
35. Molassiotis A, Charalambous A, Taylor P, et al: The effect of resistance inspiratory muscle training in the management of breathlessness in patients with thoracic malignancies: A feasibility randomised trial. Support Care Cancer 23:1637-1645, 2015
36. Moore S, Corner J, Haviland J, et al: Nurse led follow up and conventional medical follow up in management of patients with lung cancer: Randomised trial. BMJ 325:1145, 2002

37. Mosher CE, Secinti E, Hirsh AT, et al: Acceptance and commitment therapy for symptom interference in advanced lung cancer and caregiver distress: A pilot randomized trial. J Pain Symptom Manage 58:632-644, 2019
38. Nakano J, Ishii K, Fukushima T, et al: Effects of transcutaneous electrical nerve stimulation on physical symptoms in advanced cancer patients receiving palliative care. Int J Rehabil Res 43:62-68, 2020
39. Nava S, Ferrer M, Esquinas A, et al: Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: A randomised feasibility trial. Lancet Oncol 14:219-227, 2013
40. Philip J, Gold M, Milner A, et al: A randomized, double-blind, crossover trial of the effect of oxygen on dyspnea in patients with advanced cancer. J Pain Symptom Manage 32:541-550, 2006
41. Ramirez R, Planas J, Escude N, et al: EEG-based analysis of the emotional effect of music therapy on palliative care cancer patients. Front Psychol 9:254, 2018
42. Rutkowska A, Jastrzebski D, Rutkowski S, et al: Exercise training in patients with non-small cell lung cancer during in-hospital chemotherapy treatment: A randomized controlled trial. J Cardiopulm Rehabil Prev 39:127-133, 2019
43. Ting FI, Estreller S, Strebel HMJ: A phase 2 randomized clinical trial on the effect of a fan blowing air on the face to relieve dyspnea in Filipino patients with terminal cancer. Asian J Oncol 6:3-9, 2020
44. Vanderbyl BL, Mayer MJ, Nash C, et al: A comparison of the effects of medical Qigong and standard exercise therapy on symptoms and quality of life in patients with advanced cancer. Support Care Cancer 25:1749-1758, 2017
45. Vickers AJ, Feinstein MB, Deng GE, et al: Acupuncture for dyspnea in advanced cancer: A randomized, placebo-controlled pilot trial [ISRCTN89462491]. BMC Palliat Care 4:5, 2005
46. Wong SL, Leong SM, Chan CM, et al: The effect of using an electric fan on dyspnea in Chinese patients with terminal cancer. Am J Hosp Palliat Care 34:42-46, 2017
47. Wyatt G, Sikorskii A, Rahbar MH, et al: Health-related quality-of-life outcomes: A reflexology trial with patients with advanced-stage breast cancer. Oncol Nurs Forum 39:568-577, 2012
48. Yorke J, Lloyd-Williams M, Smith J, et al: Management of the respiratory distress symptom cluster in lung cancer: A randomised controlled feasibility trial. Support Care Cancer 23:3373-3384, 2015
49. Aabom B, Laier G, Christensen PL, et al: Oral morphine drops for prompt relief of breathlessness in patients with advanced cancer: A randomized, double blinded, crossover trial of morphine sulfate oral drops vs. morphine hydrochloride drops with ethanol (red morphine drops). Support Care Cancer 28: 3421-3428, 2020
50. Allard P, Lamontagne C, Bernard P, et al: How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial. J Pain Symptom Manage 17:256-265, 1999
51. Bruera E, MacEachern T, Ripamonti C, et al: Subcutaneous morphine for dyspnea in cancer patients. Ann Intern Med 119:906-907, 1993
52. Bruera E, Sala R, Spruyt O, et al: Nebulized versus subcutaneous morphine for patients with cancer dyspnea: A preliminary study. J Pain Symptom Manage 29:613-618, 2005
53. Charles MA, Reymond L, Israel F: Relief of incident dyspnea in palliative cancer patients: A pilot, randomized, controlled trial comparing nebulized hydromorphone, systemic hydromorphone, and nebulized saline. J Pain Symptom Manage 36:29-38, 2008
54. Gamborg H, Riis J, Christrup L, et al: Effect of intraoral and subcutaneous morphine on dyspnea at rest in terminal patients with primary lung cancer or lung metastases. J Opioid Manag 9:269-274, 2013
55. Hardy J, Randall C, Pinkerton E, et al: A randomised, double-blind controlled trial of intranasal midazolam for the palliation of dyspnoea in patients with life-limiting disease. Support Care Cancer 24:3069-3076, 2016
56. Hui D, Hernandez F, Larsson L, et al: Prophylactic fentanyl sublingual spray for episodic exertional dyspnea in cancer patients: A pilot double-blind randomized controlled trial. J Pain Symptom Manage 58:605-613, 2019
57. Hui D, Kilgore K, Frisbee-Hume S, et al: Effect of prophylactic fentanyl buccal tablet on episodic exertional dyspnea: A pilot double-blind randomized controlled trial. J Pain Symptom Manage 54:798-805, 2017
58. Hui D, Kilgore K, Frisbee-Hume S, et al: Dexamethasone for dyspnea in cancer patients: A pilot double-blind, randomized, controlled trial. J Pain Symptom Manage 52:8-16.e1, 2016
59. Hui D, Kilgore K, Park M, et al: Impact of prophylactic fentanyl pectin nasal spray on exercise-induced episodic dyspnea in cancer patients: A double-blind, randomized controlled trial. J Pain Symptom Manage 52:459-468.e1, 2016
60. Hui D, Xu A, Frisbee-Hume S, et al: Effects of prophylactic subcutaneous fentanyl on exercise-induced breakthrough dyspnea in cancer patients: A preliminary double-blind, randomized, controlled trial. J Pain Symptom Manage 47:209-217, 2014
61. Navigante AH, Castro MA, Cerchietti LC: Morphine versus midazolam as upfront therapy to control dyspnea perception in cancer patients while its underlying cause is sought or treated. J Pain Symptom Manage 39:820-830, 2010
62. Navigante AH, Cerchietti LC, Castro MA, et al: Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. J Pain Symptom Manage 31:38-47, 2006
63. Peoples AR, Bushunow PW, Garland SN, et al: Buspirone for management of dyspnea in cancer patients receiving chemotherapy: A randomized placebo-controlled URCC CCOP study. Support Care Cancer 24:1339-1347, 2016
64. Pinna M, Bruera E, Moralo MJ, et al: A randomized crossover clinical trial to evaluate the efficacy of oral transmucosal fentanyl citrate in the treatment of dyspnea on exertion in patients with advanced cancer. Am J Hosp Palliat Care 32:298-304, 2015
65. Simon ST, Kloke M, Alt-Epping B, et al: EffenDys-fentanyl buccal tablet for the relief of episodic breathlessness in patients with advanced cancer: A multicenter, open-label, randomized, morphine-controlled, crossover, phase II trial. J Pain Symptom Manage 52:617-625, 2016
66. Tian C, Wang JY, Wang ML, et al: Morphine versus methylprednisolone or aminophylline for relieving dyspnea in patients with advanced cancer in China: A retrospective study. SpringerPlus 5:1945, 2016
67. Gottlieb M, Mellemgaard A, Marsaa K, et al: Optimizing COPD treatment in patients with lung- or head and neck cancer does not improve quality of life: A randomized, pilot, clinical trial. Eur Clin Respir J 7:1731277, 2020
68. Minchom A, Punwani R, Filshie J, et al: A randomised study comparing the effectiveness of acupuncture or morphine versus the combination for the relief of dyspnoea in patients with advanced non-small cell lung cancer and mesothelioma. Eur J Cancer 61:102-110, 2016
69. Hui D, Morgado M, Vidal M, et al: Dyspnea in hospitalized advanced cancer patients: Subjective and physiologic correlates. J Palliat Med 16:274-280, 2013
70. Gift AG: Validation of a vertical visual analogue scale as a measure of clinical dyspnea. Rehabil Nurs 14:323-325, 1989
71. Gift AG, Narsavage G: Validity of the numeric rating scale as a measure of dyspnea. Am J Crit Care 7:200-204, 1998

72. Johnson MJ, Close L, Gillon SC, et al: Use of the modified Borg scale and numerical rating scale to measure chronic breathlessness: A pooled data analysis. Eur Respir J 47:1861-1864, 2016
73. Kirkova J, Walsh D, Rybicki L, et al: Symptom severity and distress in advanced cancer. Palliat Med 24:330-339, 2010
74. Bruera E, Kuehn N, Miller MJ, et al: The Edmonton Symptom Assessment System (ESAS): A simple method for the assessment of palliative care patients. J Palliat Care 7:6-9, 1991
75. Hui D, Bruera E: The Edmonton Symptom Assessment System 25 years later: Past, present and future developments. J Pain Symptom Manage 53:630-643, 2017
76. Mahler DA, Wells CK: Evaluation of clinical methods for rating dyspnea. Chest 93:580-586, 1988
77. Hui D, Park M, Shamieh O, et al: Personalized symptom goals and response in patients with advanced cancer. Cancer 22:1774-1781, 2016
78. Mercadante S, Adile C, Aielli F, et al: Personalized goal for dyspnea and clinical response in advanced cancer patients. J Pain Symptom Manage 57:79-85, 2019
79. Campbell ML, Templin T, Walch J: Patients who are near death are frequently unable to self-report dyspnea. J Palliat Med 12:881-884, 2009
80. Campbell ML: Psychometric testing of a respiratory distress observation scale. J Palliat Med 11:44-50, 2008
81. Campbell ML, Kero KK, Templin TN: Mild, moderate, and severe intensity cut-points for the Respiratory Distress Observation Scale. Heart Lung 46:14-17, 2017
82. Campbell ML, Templin T, Walch J: A Respiratory Distress Observation Scale for patients unable to self-report dyspnea. J Palliat Med 13:285-290, 2010
83. Campbell ML, Templin TN: Intensity cut-points for the Respiratory Distress Observation Scale. Palliat Med 29:436-442, 2015
84. Zhuang Q, Yang GM, Neo SH, et al: Validity, reliability and diagnostic accuracy of the Respiratory Distress Observation Scale for assessment of dyspnea in adult palliative care patients. J Pain Symptom Manage 57:304-310, 2019
85. Sandham MH, Medvedev ON, Hedgecock E, et al: A Rasch analysis of the Integrated Palliative Care Outcome Scale. J Pain Symptom Manage 57:290-296, 2019
86. Simon ST, Weingartner V, Higginson IJ, et al: Definition, categorization, and terminology of episodic breathlessness: Consensus by an international Delphi survey. J Pain Symptom Manage 47:828-838, 2014
87. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 166:111-117, 2002
88. Booth S, Adams L: The shuttle walking test: A reproducible method for evaluating the impact of shortness of breath on functional capacity in patients with advanced cancer. Thorax 56:146-150, 2001
89. Clive AO, Jones HE, Bhatnagar R, et al: Interventions for the management of malignant pleural effusions: A network meta-analysis. Cochrane Database Syst Rev 5:CD010529, 2016
90. Amjadi K, Voduc N, Cruysberghs Y, et al: Impact of interventional bronchoscopy on quality of life in malignant airway obstruction. Respiration 76:421-428, 2008
91. Bezjak A, Tu D, Seymour L, et al: Symptom improvement in lung cancer patients treated with erlotinib: Quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 24:3831-3837, 2006
92. Hashimoto N, Matsuzaki A, Okada Y, et al: Clinical impact of prevalence and severity of COPD on the decision-making process for therapeutic management of lung cancer patients. BMC Pulm Med 14:14, 2014
93. Wang W, Dou S, Dong W, et al: Impact of COPD on prognosis of lung cancer: From a perspective on disease heterogeneity. Int J Chron Obstruct Pulmon Dis 13: 3767-3776, 2018
94. Ytterstad E, Moe PC, Hjalmarsen A: COPD in primary lung cancer patients: Prevalence and mortality. Int J Chron Obstruct Pulmon Dis 11:625-636, 2016
95. Correction to: 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: An update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on clinical practice guidelines and the Heart Failure Society of America. Circulation 134:e298, 2016
96. Nici L, Mammen MJ, Charbek E, et al: Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 201:e56-e69, 2020
97. Collier A, Breaden K, Phillips JL, et al: Caregivers' perspectives on the use of long term oxygen therapy for the treatment of refractory breathlessness: A qualitative study. J Pain Symptom Manage 53:33-39, 2017
98. Higginson IJ, Bausewein C, Reilly CC, et al: An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: A randomised controlled trial. Lancet Respir Med 2:979-987, 2014
99. Temel JS, Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733-742, 2010
100. Zimmermann C, Swami N, Krzyzanowska M, et al: Early palliative care for patients with advanced cancer: A cluster-randomised controlled trial. Lancet 383: 1721-1730, 2014
101. Hui D, Hannon BL, Zimmermann C, et al: Improving patient and caregiver outcomes in oncology: Team-based, timely, and targeted palliative care. CA Cancer J Clin 68:356-376, 2018
102. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017
103. Hui D, Masanori M, Watanabe S, et al: Referral criteria for outpatient specialty palliative cancer care: An international consensus. Lancet Oncol 17:e552-e559, 2016
104. Paiva CE, Paiva BSR, Menezes D, et al: Development of a screening tool to improve the referral of patients with breast and gynecological cancer to outpatient palliative care. Gynecol Oncol 158:153-157, 2020
105. Hui D, Bruera E: Models of palliative care delivery for patients with cancer. J Clin Oncol 38:852-865, 2020
106. Hui D, De La Rosa A, Chen J, et al: State of palliative care services at US cancer centers: An updated national survey. Cancer 126:2013-2023, 2020
107. Bausewein C, Booth S, Gysels M, et al: Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. Cochrane Database Syst Rev 2:CD005623, 2011
108. Galbraith S, Fagan P, Perkins P, et al: Does the use of a hand-held fan improve chronic dyspnea? A randomized, controlled, crossover trial. J Pain Symptom Manage 39:831-838, 2010
109. Luckett T, Phillips J, Johnson MJ, et al: Contributions of a hand-held fan to self-management of chronic breathlessness. Eur Respir J 50:1700262, 2017
110. Barnes-Harris M, Allgar V, Booth S, et al: Battery operated fan and chronic breathlessness: Does it help? BMJ Support Palliat Care 9:478-481, 2019

111. Swan F, Newey A, Bland M, et al: Airflow relieves chronic breathlessness in people with advanced disease: An exploratory systematic review and meta-analyses. Palliat Med 33:618-633, 2019
112. Wen Z, Wang W, Zhang H, et al: Is humidified better than non-humidified low-flow oxygen therapy? A systematic review and meta-analysis. J Adv Nurs 73: 2522-2533, 2017
113. Campbell ML, Yarandi H, Dove-Medows E: Oxygen is nonbeneficial for most patients who are near death. J Pain Symptom Manage 45:517-523, 2013
114. Abernethy AP, McDonald CF, Frith PA, et al: Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: A double-blind, randomised controlled trial. Lancet 376:784-793, 2010
115. Uronis H, McCrory DC, Samsa G, et al: Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease. Cochrane Database Syst Rev 6: CD006429, 2011
116. Dysart K, Miller TL, Wolfson MR, et al: Research in high flow therapy: Mechanisms of action. Respir Med 103:1400-1405, 2009
117. Pisani L, Vega ML: Use of nasal high flow in stable COPD: Rationale and physiology. COPD 14:346-350, 2017
118. Curtis JR, Cook DJ, Sinuff T, et al: Noninvasive positive pressure ventilation in critical and palliative care settings: Understanding the goals of therapy. Crit Care Med 35:932-939, 2007
119. Quill CM, Quill TE: Palliative use of noninvasive ventilation: Navigating murky waters. J Palliat Med 17:657-661, 2014
120. Holland AE, Hill CJ, Jones AY, et al: Breathing exercises for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 10:CD008250, 2012
121. Tan SB, Liam CK, Pang YK, et al: The effect of 20-minute mindful breathing on the rapid reduction of dyspnea at rest in patients with lung diseases: A randomized controlled trial. J Pain Symptom Manage 57:802-808, 2019
122. Booth S, Moffat C, Burkin J, et al: Nonpharmacological interventions for breathlessness. Curr Opin Support Palliat Care 5:77-86, 2011
123. Bredin M, Corner J, Krishnasamy M, et al: Multicentre randomised controlled trial of nursing intervention for breathlessness in patients with lung cancer. BMJ 318:901-904, 1999
124. Chen YJ, Li XX, Ma HK, et al: Exercise training for improving patient-reported outcomes in patients with advanced-stage cancer: A systematic review and meta-analysis. J Pain Symptom Manage 59:734-749.e10, 2020
125. McCarthy B, Casey D, Devane D, et al: Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2:CD003793, 2015
126. Barnes H, McDonald J, Smallwood N, et al: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database Syst Rev 3:CD011008, 2016
127. Ekström M, Bajwah S, Bland JM, et al: One evidence base; three stories: Do opioids relieve chronic breathlessness? Thorax 73:88-90, 2018
128. Luo N, Tan S, Li X, et al: Efficacy and safety of opioids in treating cancer-related dyspnea: A systematic review and meta-analysis based on randomized controlled trials. J Pain Symptom Manage 61:198-210.e1, 2021
129. Spaner D: Effectiveness of the buccal mucosa route for methadone administration at the end of life. J Palliat Med 17:1262-1265, 2014
130. Boyden JY, Connor SR, Otolorin L, et al: Nebulized medications for the treatment of dyspnea: A literature review. J Aerosol Med Pulm Drug Deliv 28:1-19, 2015
131. Hui D, Bruera E: Use of short-acting opioids in the management of breathlessness: An evidence-based review. Curr Opin Support Palliat Care 14:167-176, 2020
132. Currow DC, McDonald C, Oaten S, et al: Once-daily opioids for chronic dyspnea: A dose increment and pharmacovigilance study. J Pain Symptom Manage 42: 388-399, 2011
133. Arthur J, Hui D: Safe opioid use: Management of opioid-related adverse effects and aberrant behaviors. Hematol Oncol Clin North Am 32:387-403, 2018
134. Paice JA, Portenoy R, Lacchetti C, et al: Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34:3325-3345, 2016
135. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols J, et al: Respiratory adverse effects of opioids for breathlessness: A systematic review and meta-analysis. Eur Respir J 50:1701153, 2017
136. Coyne PJ, Viswanathan R, Smith TJ: Nebulized fentanyl citrate improves patients' perception of breathing, respiratory rate, and oxygen saturation in dyspnea. J Pain Symptom Manage 23:157-160, 2002
137. Mori M, Morita T, Matsuda Y, et al: How successful are we in relieving terminal dyspnea in cancer patients? A real-world multicenter prospective observational study. Support Care Cancer 28:3051-3060, 2020
138. Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, et al: Safety of benzodiazepines and opioids in very severe respiratory disease: National prospective study. BMJ 348:g445, 2014
139. Dowell D, Haegerich TM, Chou R: CDC guideline for prescribing opioids for chronic pain-United States, 2016. JAMA 315:1624-1645, 2016
140. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al: Reduction of cancer-related fatigue with dexamethasone: A double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol 31:3076-3082, 2013
141. Chow E, Meyer RM, Ding K, et al: Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases: A double-blind, randomised placebo-controlled, phase 3 trial. Lancet Oncol 16:1463-1472, 2015
142. Elsayem A, Bruera E: High-dose corticosteroids for the management of dyspnea in patients with tumor obstruction of the upper airway. Support Care Cancer 15:1437-1439, 2007
143. Lin RJ, Adelman RD, Mehta SS: Dyspnea in palliative care: Expanding the role of corticosteroids. J Palliat Med 15:834-837, 2012
144. Mori M, Shirado AN, Morita T, et al: Predictors of response to corticosteroids for dyspnea in advanced cancer patients: A preliminary multicenter prospective observational study. Support Care Cancer 25:1169-1181, 2017
145. Arbour KC, Mezquita L, Long N, et al: Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. J Clin Oncol 36:2872-2878, 2018
146. Ricciuti B, Dahlberg SE, Adeni A, et al: Immune checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus nonpalliative indications. J Clin Oncol 37:1927-1934, 2019
147. Agabiti N, Corbo GM: COPD and bronchodilators: Should the heart pay the bill for the lung? Eur Respir J 49:1700370, 2017
148. Currow DC, Ekstrom M, Louw S, et al: Sertraline in symptomatic chronic breathlessness: A double blind, randomised trial. Eur Respir J 53:1801270, 2019
149. Borson S, McDonald GJ, Gayle T, et al: Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. Psychosomatics 33:190-201, 1992
150. Lacasse Y, Beaudoin L, Rousseau L, et al: Randomized trial of paroxetine in end-stage COPD. Monaldi Arch Chest Dis 61:140-147, 2004
151. Eiser N, Harte R, Spiros K, et al: Effect of treating depression on quality-of-life and exercise tolerance in severe COPD. COPD 2:233-241, 2005

152. Ström K, Boman G, Pehrsson K, et al: Effect of protriptyline, 10 mg daily, on chronic hypoxaemia in chronic obstructive pulmonary disease, Eur Respir J 8: 425-429, 1995
153. Light RW, Stansbury DW, Webster JS: Effect of 30 mg of morphine alone or with promethazine or prochlorperazine on the exercise capacity of patients with COPD. Chest 109:975-981, 1996
154. O'Neill PA, Morton PB, Stark RD: Chlorpromazine: A specific effect on breathlessness? Br J Clin Pharmacol 19:793-797, 1985
155. Rice KL, Kronenberg RS, Hedemark LL, et al: Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction. Br J Dis Chest 81:287-292, 1987
156. Stone P, Rix, Kurowska A, et al: Re: Nebulized furosemide for dyspnea in terminal cancer patients. J Pain Symptom Manage 24:274-275, 2002; author reply 275-276
157. Wilcock A, Walton A, Manderson C, et al: Randomised, placebo controlled trial of nebulised furosemide for breathlessness in patients with cancer. Thorax 63: 872-875, 2008
158. Maltoni M, Scarpi E, Rosati M, et al: Palliative sedation in end-of-life care and survival: A systematic review. J Clin Oncol 30:1378-1383, 2012
159. Maeda I, Morita T, Yamaguchi T, et al: Effect of continuous deep sedation on survival in patients with advanced cancer (J-Proval): A propensity score-weighted analysis of a prospective cohort study. Lancet Oncol 17:115-122, 2016
160. Kirk TW, Mahon MM: National Hospice and Palliative Care Organization (NHPCO) position statement and commentary on the use of palliative sedation in imminently dying terminally ill patients. J Pain Symptom Manage 39:914-923, 2010
161. Mahler DA, Sethi S: Enhanced drug and device development by "targeting relief of dyspnea." Chest 158:464-466, 2020
162. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol 35: 3618-3632, 2017
163. Johnson MJ, Kanaan M, Richardson G, et al: A randomised controlled trial of three or one breathing technique training sessions for breathlessness in people with malignant lung disease. BMC Med 13:213, 2015
164. Bevans M, Sternberg EM: Caregiving burden, stress, and health effects among family caregivers of adult cancer patients. JAMA 307:398-403, 2012
165. Booth S, Silvester S, Todd C: Breathlessness in cancer and chronic obstructive pulmonary disease: Using a qualitative approach to describe the experience of patients and carers. Palliat Support Care 1:337-344, 2003
166. Hutchinson A, Barclay-Klingle N, Galvin K, et al: Living with breathlessness: A systematic literature review and qualitative synthesis. Eur Respir J 51:1701477, 2018
167. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2013. Bethesda, MD, National Cancer Institute. http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016, 2016
168. Mead H, Cartwright-Smith L, Jones K, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, NY, The Commonwealth Fund, 2008
169. American Cancer Society: Cancer Facts & Figures for African Americans 2019-2021. https://www.cancer.org/research/cancer-facts-statistics/cancer-facts-figures-for-african-americans.html, 2019
170. Patel MI, Lopez AM, Blackstock W, et al: Cancer disparities and health equity: A policy statement from the American Society of Clinical Oncology. J Clin Oncol 38:3439-3448, 2020
171. Lathan CS, Cronin A, Tucker-Seeley R, et al: Association of financial strain with symptom burden and quality of life for patients with lung or colorectal cancer. J Clin Oncol 34:1732-1740, 2016
172. Barkhudaryan A, Scherbakov N, Springer J, et al: Cardiac muscle wasting in individuals with cancer cachexia. ESC Heart Fail 4:458-467, 2017
173. Hui D, Naberhuis J, Dibaj S, et al: Association between plasma brain natriuretic peptide and overall survival in patients with advanced cancer: Preliminary findings. J Pain Symptom Manage 58:465-471, 2019
174. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. J Clin Oncol 34:2925-2934, 2016
175. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 33:2563-2577, 2015
176. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 32: 306-311, 2014
177. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. J Oncol Pract 7:46s-51s, 2011
178. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. J Clin Oncol 27:3868-3874, 2009
179. Hui D, Glitza I, Chisholm G, et al: Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer 119: 1098-1105, 2012
180. American Cancer Society: Understanding Advanced Cancer, Metastatic Cancer, and Bone Metastasis. https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html
181. Opioid Overdose: Guideline Overview. Atlanta, GA, Centers for Disease Control and Prevention, 2020
182. Rochwerg B, Brochard L, Elliott MW, et al: Official ERS/ATS clinical practice guidelines: Noninvasive ventilation for acute respiratory failure. Eur Respir J 50: 1602426, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Dyspnea in Advanced Cancer: ASCO Guideline

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

David Hui
Research Funding: Helsinn Healthcare

Toby C. Campbell
Consulting or Advisory Role: Heron
Other Relationship: Agrace Hospice & Palliative Care

David C. Currow
Consulting or Advisory Role: Mayne Pharma, Specialised Therapeutics, Helsinn Healthcare
Patents, Royalties, Other Intellectual Property: Intellectual Property—Mayne Pharma
Travel, Accommodations, Expenses: Helsinn Therapeutics

Masanori Mori
Honoraria: Shionogi, Chugai Pharma, Kyowa Hakko Kirin, Daiichi Sankyo, Lilly Japan

Stefano Nava
Consulting or Advisory Role: Breas

Eric J. Roeland
Consulting or Advisory Role: Napo Pharmaceuticals, AIM Specialty Health, Oragenics, BASF, Vector Oncology, Asahi Kasei, Heron, Pfizer/EMD Serono, Astellas Pharma, Helsinn Therapeutics
Expert Testimony: Regents of the University of California

Declan Walsh
Leadership: Nualtra
Stock and Other Ownership Interests: Nualtra
Honoraria: Helsinn Therapeutics
Consulting or Advisory Role: Helsinn Therapeutics
Research Funding: Nualtra

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Management of Dyspnea in Advanced Cancer: ASCO Guideline Expert Panel Membership

Name	Affiliation or Institution	Area of Expertise
David Hui, MD (cochair)	MD Anderson Cancer Center, Houston, TX	Medical oncology and palliative care
Margaret L. Campbell, PhD, RN (cochair)	Wayne State University, Detroit, MI	Palliative care
Ting Bao, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Breast oncology and integrative medicine
Toby C. Campbell, MD, MS	University of Wisconsin-Madison, Madison, WI	Medical oncology and palliative care
Patrick J. Coyne, MSN, ACHPN, ACNS-BC	Medical University of South Carolina, Charleston, SC	Palliative care
David C. Currow, BMed, MPH, PhD	University of Technology Sydney, Sydney, Australia	Palliative care
Arjun Gupta, MD	Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD	Medical oncology
Aliza L. Leiser, MD	Rutgers RWJ Cancer Institute of New Jersey, New Brunswick, NJ	Gynecologic oncology, PGIN representative
Masanori Mori, MD	Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan	Palliative care
Stefano Nava, MD	IRCCS Azienda Ospedaliera University of Bologna, S. Orsola-Malpighi Hospital, Alma Mater University, Bologna, Italy	Respiratory medicine
Lynn F. Reinke, PhD, ARNP	VA Puget Sound Health Care System, Seattle, WA	Palliative care and respiratory medicine
Eric J. Roeland, MD	Massachusetts General Hospital Cancer Center, Boston, MA	Medical oncology and palliative care
Carole Seigel	Brookline, MA	Advocacy
Declan Walsh, MD, MSc	Levine Cancer Institute, Charlotte, NC	Medical oncology and palliative care
Kari Bohlke, ScD	ASCO	ASCO practice guideline staff (health research methods)

Abbreviation: PGIN, Practice Guidelines Implementation Network.