

Management of Dyspnea in Advanced Cancer: ASCO Guideline

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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 non-pharmacologic 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.

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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 intensity¹ (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.

ASSOCIATED CONTENT

Appendix

Data Supplement

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

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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, $\text{SpO}_2 \leq 90\%$ on room air) (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).
- 4.3. Supplemental oxygen is not recommended when $\text{SpO}_2 > 90\%$ (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	$\text{PaCO}_2 \geq 45$ 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 oxycodone, 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

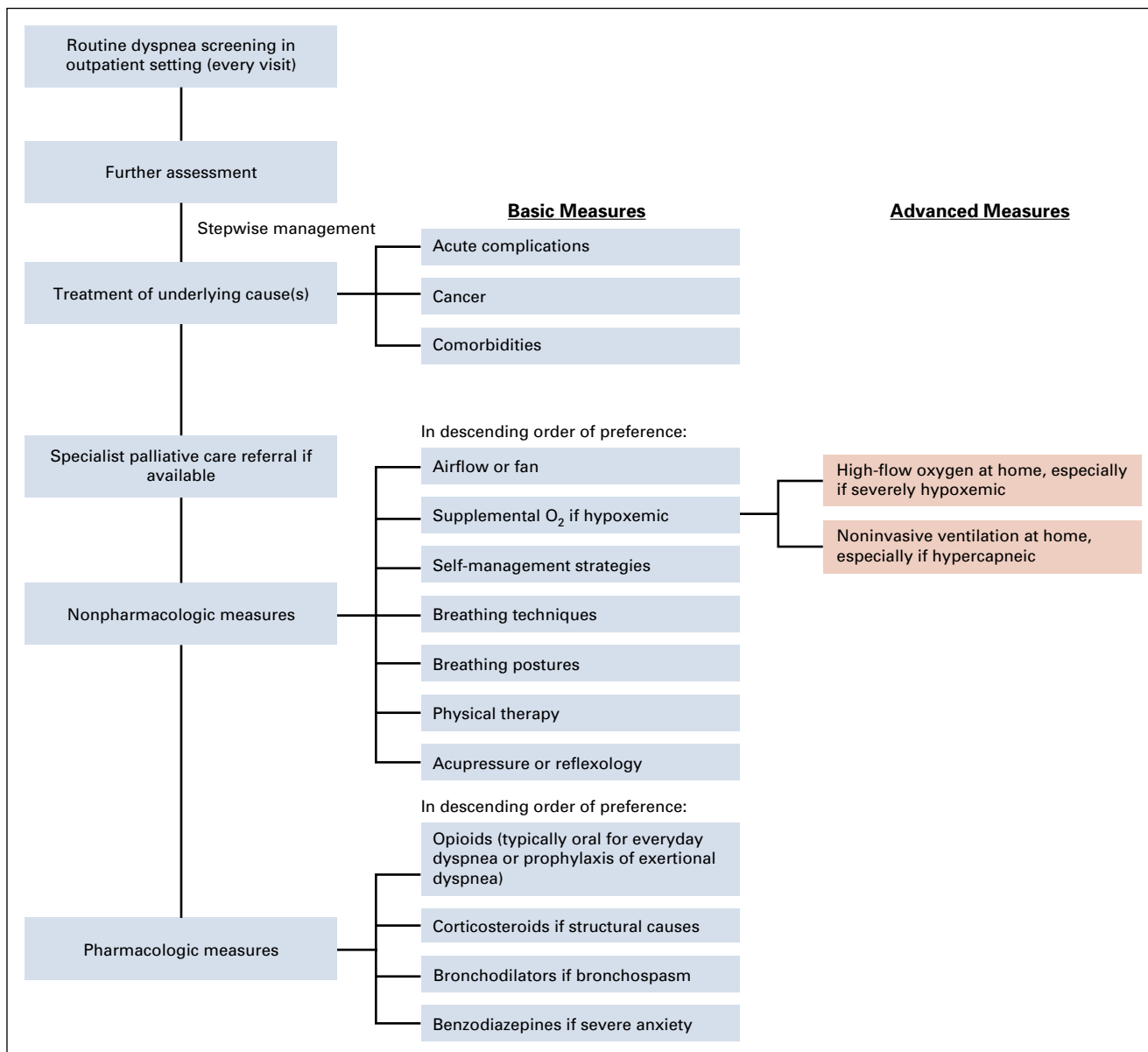


FIG 1. Outpatient management of chronic dyspnea. In the ambulatory setting, patients may present with chronic dyspnea that may limit their daily activities. A hierarchical approach is recommended to introduce interventions in a stepwise manner to include treatment of reversible causes, a palliative care 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.

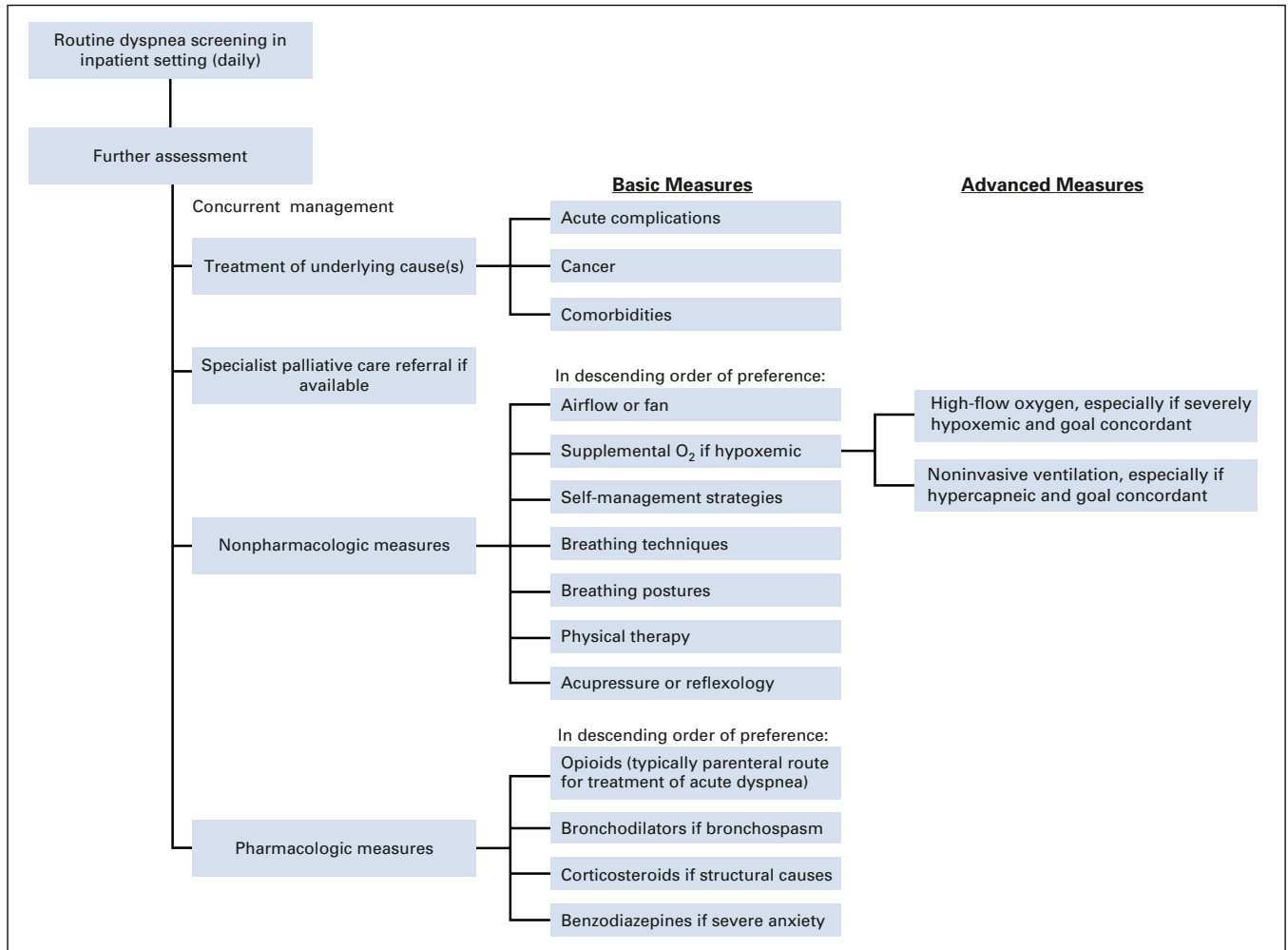


FIG 2. Inpatient management of acute severe dyspnea. In the hospital setting, patients may report acute dyspnea, which requires more urgent attention. Instead of a stepwise trial, clinicians may consider a concurrent approach to treat any reversible causes while providing palliation. Under close monitoring, 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 coauthors 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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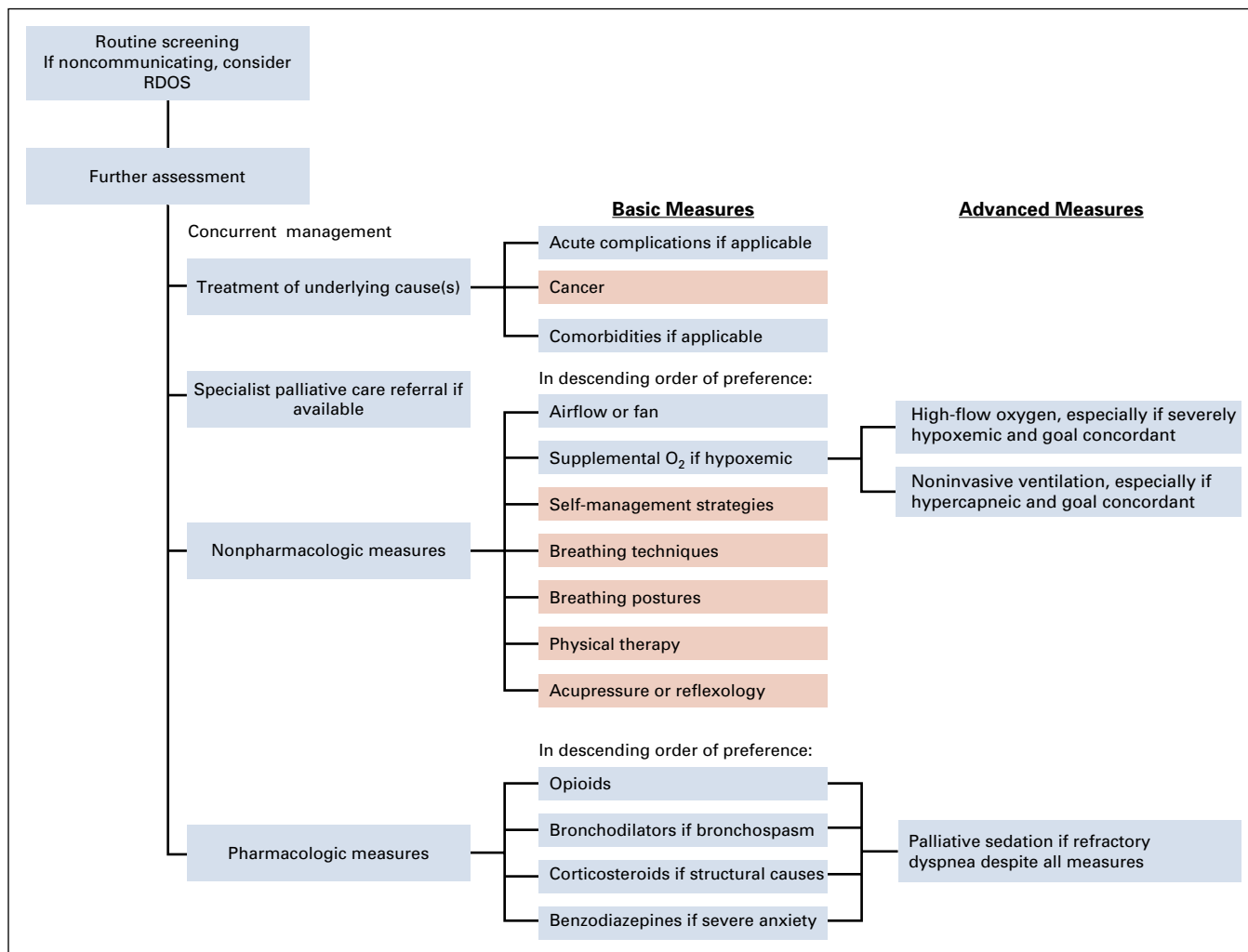


FIG 3. Inpatient management of patients with dyspnea in the last days of life. Patients in the last days of life often have severe dyspnea requiring hospitalization. A palliative care consultation is essential. Delirium and drowsiness may complicate symptom assessment and goals-of-care discussions. The 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

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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 reviews¹⁵⁻¹⁸ 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 interventions²⁰⁻⁴⁸; 17 RCTs and 1 retrospective cohort study (1,224 patients) addressed the comparative benefits of pharmacologic interventions⁴⁹⁻⁶⁶; and two RCTs (287 patients) addressed the comparative benefits of non-pharmacologic, 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 Society¹ and the

European Society for Medical Oncology¹⁹ 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 RCT³⁹), 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 nonhumidified 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 SpO₂ 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 cmH₂O) and then gradually increase as tolerated. Expiratory pressure should never be above 6-8 cmH₂O 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 training¹²⁴ 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 non-pharmacologic 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 RCTs⁴⁹⁻⁶⁵ 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-naïve, 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-naïve, 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-naïve, 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 guideline¹³⁴) 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 cm³ 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](https://clinicaltrials.gov/ct2/show/study/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. Non-pharmacologic 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 SpO₂ > 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 Cancers¹³⁴ (<https://ascopubs.org/doi/full/10.1200/JCO.2016.68.5206>)
- Integration of Palliative Care into Standard Oncology Practice¹⁰² (<http://ascopubs.org/doi/10.1200/JCO.2016.70.1474>)
- Patient-Clinician Communication¹⁶² (<http://ascopubs.org/doi/10.1200/JCO.2017.75.2311>)

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EQUAL CONTRIBUTION

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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

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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.