

Management of Refractory Breathlessness: a Review for General Internists



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Internists frequently care for patients who suffer from breathlessness in both the inpatient and the outpatient settings. Patients may experience chronic refractory breathlessness despite thorough evaluation and management of their underlying medical illnesses. Left unmanaged, chronic breathlessness is associated with worsened quality of life, more frequent visits to the emergency room, and decreased activity levels, as well as increased levels of depression and anxiety. This narrative review summarizes recent research on interventions for the relief of breathlessness, including both non-pharmacologic and pharmacologic options.

KEY WORDS: dyspnea; breathlessness; chronic disease management.

J Gen Intern Med 36(4):1035–40

DOI: 10.1007/s11606-020-06439-0

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Dyspnea, or breathlessness, is defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.”¹ Distinct sensations that patients experience may be categorized as work or effort of breathing, chest tightness, and air hunger or unsatisfied inspiration.² Breathlessness is a common symptom for patients in both the inpatient and the outpatient settings. Large community surveys estimate that 25% of community-dwelling adults older than 70 experience dyspnea with some regularity³ while 9–11% of community-dwelling adults experience chronic, refractory breathlessness.^{4,5} Chronic breathlessness is defined as breathlessness at rest or that limits activities despite optimal medical management of the underlying disease process.⁶ The prevalence of refractory breathlessness increases with increasing level of medical care, patient age, and stage of illness. A cross-sectional population-based survey study of 1404 randomly selected patients 70 years old or older found that the prevalence of breathlessness increased with advancing age with 32.3% of all subjects over the age of 70 and 45.3% of men and 41.8% of women over the age of 80 experiencing this symptom.⁷ A study of patients with chronic lung disease or lung cancer found that breathlessness occurred

in 94% and 78% respectively during the final year of life.⁸ The presence of chronic breathlessness portends higher risk of mortality in patients with COPD and heart disease, and in the elderly.⁹

Despite being a common concern for patients, chronic breathlessness is under-recognized by clinicians.¹⁰ Left unmanaged, chronic dyspnea can have profound impacts on patients including worsened quality of life, more frequent visits to the emergency room, decreased activity levels, increased social isolation, and worsened family well-being.^{6,11–13} For older patients with COPD, chronic dyspnea is one of the most important factors limiting the ability to complete daily activities.¹⁴ Chronic dyspnea is also associated with increased levels of depression, anxiety, and spiritual distress.^{6,13}

The first step in dyspnea management is to evaluate for the underlying medical etiology and initiate appropriate disease-targeting therapies. Pulmonary or cardiac disease processes are the most common causes of chronic dyspnea, although other conditions may also present with chronic breathlessness (Table 1). An understanding of the physiologic mechanisms that result in the sensation of breathlessness is helpful for determining potential causes and for management of the symptom itself.

BIOLOGY OF BREATHLESSNESS

Although breathlessness may result from a diverse group of disease states, it always reflects a disruption in the balance between inspiratory drive and ventilatory capacity.¹² The somatosensory cortex integrates data about the inspiratory drive from the medullary respiratory centers as well as information about respiratory function from chemoreceptors (which detect variations in pO₂ and pCO₂) and peripheral mechanoreceptors in the lungs and respiratory muscles (which detect stretch or motor activity).¹⁵ In healthy individuals, as inspiratory drive intensifies (such as during exercise), medullary respiratory centers relay this heightened need to both the respiratory muscles as well as a corollary message to the somatosensory cortex. Ventilation increases and the degree of augmented activity is relayed via the peripheral mechanoreceptors to the somatosensory cortex.¹ The somatosensory cortex interprets this as equipoise between respiratory drive and performance so there is no associated discomfort. For patients with breathlessness, the respiratory drive from the medullary centers is

Received April 24, 2020

Accepted December 10, 2020

Published online January 19, 2021

Table 1 Causes of Chronic Refractory Breathlessness

Pulmonary	Chronic obstructive pulmonary disease
	Bronchiectasis
	Asthma
	Tracheomalacia
	Interstitial lung disease
	Cancer
	Chronic pulmonary embolic disease
	Pulmonary hypertension
	Vasculitis
	Pleural effusion
Cardiac	Heart failure
	Ischemic heart disease
	Arrhythmia
	Valvular heart disease
Neuromuscular disease	Constrictive pericarditis
	Amyotrophic lateral sclerosis
	Myasthenia gravis
Other	Guillain-Barre syndrome
	Chest wall deformities
	Upper airway compression
	Vocal cord dysfunction
	Obesity
	Deconditioning
	Anemia
Anxiety	

inadequately addressed. This may be secondary to triggers for increasing respiratory drive (i.e., hypercapnia, hypoxia, acidosis) and/or due to a decline in pulmonary function or worsening muscle weakness.¹ The peripheral chemoreceptors and/or mechanoreceptors send afferent inputs back to the somatosensory cortex reflecting this underperformance. The somatosensory cortex perceives this unmet need as respiratory discomfort.¹

In addition to the physical sensation of breathlessness, there is a significant affective component for many patients. Studies using functional magnetic resonance imaging (fMRI) demonstrate that inducing dyspnea leads to activation of the limbic and paralimbic systems which can result in anxiety, panic, and affective distress.¹⁶ These emotional centers are activated by the anticipation of dyspnea as well, providing further evidence for the role of affective processing for influencing patient experiences.¹⁶ As a result, patients with comparable severity of pulmonary dysfunction may describe very different degrees of dyspnea.¹⁷

The affective processing of dyspnea impacts the approach to this symptom in the broader context of patients' quality of life. As aforementioned, patients with chronic dyspnea have higher rates of depression and anxiety.⁶ Conversely, uncontrolled anxiety can worsen dyspnea.¹⁸ The American Thoracic Society guidelines on assessing and managing dyspnea recommend considering distinct domains: sensory-perceptual experience, affective distress, and symptom/disease impact or burden.¹ When treating patients with refractory breathlessness, it is helpful to keep these distinct components in mind as each can drive dyspnea alone or they may also work in concert to exacerbate this symptom. Recognizing this dynamic will allow clinicians to provide better symptom control as well as education for patients to help them better understand their symptoms.

EVALUATION OF BREATHLESSNESS

Chronic refractory breathlessness may be the consequence of a range of diseases (see Table 1) and requires thoughtful evaluation that begins with the history and physical exam. Similarly to obtaining a detailed description of pain, eliciting details about the character of dyspnea is useful in considering the differential diagnosis, workup, and treatment options. The Multidimensional Dyspnea Profile provides a framework for assessment of breathlessness that includes the degree of unpleasantness or discomfort of breathing sensations (ranging from 0 to 10 where 0 is no discomfort to 10 indicating unbearable), sensory quality (effort, air hunger, tightness, mental effort, breathing a lot), and intensity of negative emotions (depressed, anxious, frustrated, angry, afraid).^{2,19} See Table 2 for a summary of common patient descriptors of breathlessness. A study of inpatients with significant dyspnea found the most common description was "air hunger" and associated emotional symptoms were anxiety and frustration.² Among patients presenting to an outpatient pulmonary clinic, patients' qualities of breathlessness varied depending on the underlying illness.¹⁹ Another study of 148 outpatients found that "chest tightness" was associated with asthma and was much less common as a descriptor among patients with COPD.²⁰ This finding may be useful in differentiating between these conditions. In addition, "shallow breathing" was associated with interstitial lung disease.

Associated symptoms are also useful in narrowing the differential diagnosis for chronic breathlessness.²¹ The absence of cough argues against COPD. Absence of throat

Table 2 Patient Descriptions of Breathlessness (Derived from Mahler, Am J Resp Crit Care Med, 1996)

Characteristic	Patient description	Associated conditions
Work/effort of breathing	"I feel out of breath" "My breathing requires effort" "My breathing requires work" "I cannot get enough air in"	COPD Asthma Interstitial lung disease Heart failure Bronchiectasis Deconditioning
Exhalation	"My breath does not go out all the way"	Heart failure
Tight	"My chest feels tight" "My chest is constricted"	Asthma Bronchiectasis
Inhalation	"My breath does not go all the way in"	Heart failure Neuromuscular illnesses
Rapid	"My breathing is rapid"	Interstitial lung disease Deconditioning Neuromuscular illnesses
Breathing more	"I feel I am breathing more"	Deconditioning
Heavy	"My breathing is heavy"	Bronchiectasis Deconditioning
Air hunger	"I feel hunger for air"	Common description for any condition as breathlessness intensifies

clearing and post-nasal drip argue against an upper airway process causing dyspnea. Orthopnea and paroxysmal nocturnal dyspnea suggest heart failure as the cause of breathlessness.

Physical examination findings (elevated jugular venous pressure, peripheral edema) are useful in detecting heart failure as a cause of chronic dyspnea while the absence of crackles on lung exam argues against heart failure.²¹ Although wheezes are not specific, their absence argues against asthma or COPD as a cause of chronic dyspnea. Fine basal inspiratory crackles are suggestive of interstitial lung disease in the absence of cardiac disease.

Initial testing in the evaluation of chronic dyspnea generally includes complete blood count, blood chemistries, thyroid function tests, B-type natriuretic peptide if there is clinical suspicion of heart failure, chest X-ray, electrocardiogram, and spirometry. These studies may be sufficient to establish a working diagnosis. An algorithmic approach to the evaluation of chronic dyspnea among patients referred to a dedicated specialist clinic found that diagnoses were established in 37% of 123 patients using these studies.²² The addition of echocardiography and full pulmonary function testing (DLCO, methacholine challenge) guided by clinical suspicion improves diagnostic yield.²³ Additional testing should be dictated by clinical suspicion and potentially subspecialty consultation and may include cardiopulmonary exercise testing, computed tomography of the chest, ventilation-perfusion lung scanning, and stress echocardiography.^{21,22,24} Table 3 provides a tiered approach to the workup of chronic breathlessness.

Before advancing to symptomatic management of refractory breathlessness, the presumed diagnosis should be carefully reconsidered if the symptom has not responded to treatment. A retrospective study of 122 patients referred to cardiology or pulmonary clinics found that diagnostic uncertainty was common.²⁵ In addition, it is critical to assess patient understanding of illness and treatment of the underlying illness (examples: inhaler technique, medication dosing), adherence to treatment including barriers such as access to medication, and social determinants of health impacting illness (examples: housing status, health literacy, health insurance, medication costs).²⁶

SYMPTOMATIC MANAGEMENT OF BREATHLESSNESS

In addition to diagnosing and treating the underlying causes of dyspnea, there are general principles that can guide management of this symptom. Table 4 provides a checklist of questions that guide the overall approach to breathlessness. Medical optimization and non-pharmacologic therapies provide unique benefits without the potential hazards inherent to the evidence-supported pharmacologic interventions for breathlessness. Pharmacologic options targeted at symptom relief should be considered only after other options have been exhausted.

Table 3 Tiered Workup for Chronic Breathlessness

Tier	Components	Diagnostic considerations
Initial	History and physical exam	Use of findings or absence of findings to narrow the differential and focus testing
Tier 1	Blood tests (hemoglobin, chemistries, TSH) BNP or NT-proBNP (if heart failure likely) Chest X-ray	Anemia Heart failure
Tier 2	Electrocardiogram Spirometry Echocardiogram (if murmur on exam or suspicion of heart failure)	Cardiopulmonary processes Cardiac processes COPD or asthma Heart failure Cardiac valvular disease
Tier 3 (guided by clinical suspicion and judgement)	Full pulmonary function testing (DLCO, methacholine challenge) High resolution CT chest Ventilation/perfusion lung scan Cardiopulmonary exercise testing	Pulmonary hypertension Asthma, COPD, interstitial lung disease Interstitial lung disease Malignancy Chronic thromboembolic disease Valuable when dyspnea is out of proportion to the known cardiac or pulmonary disease Helpful in supporting deconditioning, obesity, or psychogenic cause of dyspnea
Subspecialty consultation	Pulmonary Cardiology Less commonly: Gastroenterology, Otolaryngology	Can be referred at any point during the workup or management but most value-based if in conjunction with or following tier 3 evaluations
Response to treatment	Guideline concordant treatment for the presumed diagnosis or diagnoses	If inadequate response, reconsider workup and need for consultation. Consider symptom management in addition to treatment of the underlying disease

MEDICAL OPTIMIZATION

Medical optimization refers to the evaluation and treatment of the organic diseases producing breathlessness. For many patients, treating the underlying disease is sufficient for symptom resolution. However, especially for patients with acute on chronic dyspnea (i.e., acute exacerbation of severe underlying heart or lung disease), this may not provide adequate symptom control.

In addition to treating the underlying medical etiologies for dyspnea, the clinician should evaluate for psychological triggers for worsening breathlessness. Depression and anxiety are both more common in patients with refractory dyspnea. These psychological comorbidities can be both triggers for and sequelae of chronic breathlessness. It is not easy for patients to

Table 4 Question Checklist for Management of Chronic Breathlessness

1. Is the cause of breathlessness well understood? Assess diagnostic certainty
2. Should additional tests be considered?
3. Is medical management of the underlying illness optimized?
a. Guideline concordant treatment? (Example: ATS practice guideline for COPD)
b. Patient access to medications?
c. Patient understanding of treatment?
d. Patient adherence to treatment?
e. Appropriate subspecialist input?
4. What role is anxiety, depression, fear playing in symptoms?
5. How are social determinants of health impacting the underlying illness, management, and symptoms?
6. Are there non-pharmacologic interventions that should be considered?
7. Would conditioning exercise or pulmonary rehabilitation potentially be beneficial?
8. Is the patient a candidate for opioid-based treatment of symptoms?
9. Are there other adjuncts (example: management of anxiety or depression) that should be considered?

differentiate these components during an acute exacerbation so it is imperative that clinicians try to identify elements of this dyspnea-anxiety cycle and help patients develop approaches to control it. Patients who receive cognitive behavioral therapy-based strategies to control their symptoms have less depression, anxiety, and dyspnea, and fewer hospitalizations.²⁷

SUPPLEMENTAL OXYGEN

Supplemental oxygen is frequently utilized in the inpatient setting. While it is clear that hypoxic patients benefit from using oxygen,²⁸ the risk/benefit analysis for oxygen use in dyspneic (but not hypoxic) patients has evolved in recent years. Although patients may report decreased dyspnea, data suggests that it is not the supplemental oxygen,²⁹ but rather the movement of air over the face that is helpful.³⁰ This is important to explain as patients and caregivers often overestimate the benefits and underestimate the risks of supplemental oxygen use.³¹

This becomes a particularly important distinction when we consider the potential harms of supplemental oxygen. Use of oxygen may mask evolving hypoxia and delay evaluation and treatment of the underlying cause. Oxygen use can limit patient mobility, even with portable tanks that can be taxing to carry or pull. Patients with chronic breathlessness are at higher risk for and suffer poorer outcomes from muscular deconditioning so limiting mobility is particularly detrimental. There are also the emotional hazards of utilizing supplemental oxygen. Patients can have worsened anxiety and social isolation about their illness as being connected to oxygen may be stigmatizing.³² Lastly, recent literature has shown that unnecessary oxygen use is actually associated with increased mortality as an inpatient and after discharge.³³ This is in contrast to the longstanding belief that supplemental oxygen is a benign intervention. Clinicians should intentionally approach this as an education opportunity for patients and their caregivers.

NON-PHARMACOLOGIC INTERVENTIONS

Following medical optimization, first-line symptomatic therapy for breathlessness should focus on non-pharmacologic interventions. These have been widely studied and include several options that clinicians can utilize in both the inpatient and outpatient settings. The intervention with the most extensive data is pulmonary rehabilitation programs. Pulmonary rehab improves dyspnea, quality of life, and anxiety for patients with chronic breathlessness from a variety of disease processes.^{15,34,35} A recent retrospective cohort study of 197,376 Medicare patients admitted to the hospital with COPD exacerbations found that only 1.5% of patients initiated pulmonary rehabilitation within 90 days of discharge.³⁶ Pulmonary rehabilitation was associated with lower risk of death during the next year (absolute risk difference – 6.7%, 95% confidence interval – 7.9 to – 5.6%). Although hospitalists cannot provide pulmonary rehabilitation during an acute inpatient stay, data suggests they miss opportunities to refer patients.³⁷ Outpatient physicians should also screen and refer patients with dyspnea to pulmonary rehabilitation when available.

In addition to ensuring a prescription for pulmonary rehabilitation at discharge, hospitalists can also work with nurses and/or physical therapists to ensure frequent mobility for admitted patients. Patients with chronic dyspnea are at increased risk for becoming debilitated because they limit their physical activity to avoid becoming dyspneic. Weakened muscles switch to anaerobic metabolism faster than healthy muscles and the resultant metabolic acidosis worsens breathlessness by increasing respiratory drive.¹⁵ Additionally, as patients become dyspneic, they must increase their respiratory rate to compensate. This increased respiratory rate leads to worsened respiratory mechanics with increased air trapping and respiratory muscles working beyond their functional capacity.¹⁵ It is imperative that hospitalized patients have the opportunity to maintain their baseline level of function to avoid this precipitous worsening of their dyspnea and quality of life.

A 2008 Cochrane review found that several interventions were beneficial for dyspnea including vibration of the chest wall, electrical stimulation of leg muscles, and walking aids.³⁸ These interventions work by optimizing the balance of effort required versus work achieved. Vibration of the chest wall is thought to alter the afferent signals from mechanoreceptors in the chest wall muscles.³⁹ Electric stimulation of leg muscles improves muscle strength and has a valuable role for patients who cannot tolerate the demands of pulmonary rehabilitation.⁴⁰ Lastly, walking aids such as walkers likely improve work of breathing by encouraging a forward leaning posture and by stabilizing the rib cage which allows the chest wall muscles to more fully engage in respiratory activity.⁴¹

Additional non-pharmacologic therapies that improve breathlessness include a mixture of educational interventions and distraction techniques. Anxiety reduction techniques

including cognitive behavioral therapy, relaxation therapy, and mindfulness exercises have been helpful.^{14,18} A recent meta-analysis found that Tai Chi resulted in significant improvement in dyspnea among patients with COPD.⁴² Breathlessness has also been improved with education on breathing techniques⁴³ as well as proper inhaler technique education for patients with COPD.⁴⁴ There is increasing data on using music as a form of distraction.⁴⁵ Lastly, there is growing data suggesting that fans directed at the face can improve symptoms without negative consequences.³⁰

PHARMACOLOGIC INTERVENTIONS

Opioids are the primary pharmacologic option for patients who have breathlessness that is refractory to disease optimization and non-pharmacologic interventions. Opioids are believed to relieve dyspnea through several pathways including decreasing the respiratory drive, altering the central processing of dyspnea, and possibly through decreasing anxiety.⁴⁶ Dyspnea and pain share neural networks so relief of both with opioids likely reflects similar mechanisms of action. Interestingly, experimental research has shown that low doses of naloxone, an opioid antagonist, increase dyspnea and decrease exercise capacity.^{47,48}

A 2016 Cochrane review demonstrated that oral and intravenous opioids improve dyspnea, but inhaled opioids are not useful.⁴⁹ Other studies have attempted to identify doses that are effective and safe in opioid-naïve patients. Safety remains a concern as opioids do carry an increased risk of mortality.⁵⁰ Many physicians are reluctant to prescribe these medications because of safety concerns, as well as a lack of knowledge and experience.⁵¹ However, low doses can be used to find a balance of safety and efficacy. A large prospective study of over 2200 patients with chronic respiratory failure found that oral morphine equivalent (OME) doses of < 30 mg a day are safe and are not associated with increased mortality.⁵⁰ As little as 10–20 mg of OME daily may be sufficient to improve dyspnea.⁵² Particularly in patients dealing with life-limiting illness, clinicians should consider starting opioids for patients with refractory dyspnea in the same way we would manage refractory pain. A recent American Thoracic Society practice guideline recommended that “opioid-based therapy be considered for dyspnea management within a personalized shared decision-making approach.”⁵³

Multiple non-opioid medications have been evaluated as potential adjuncts for dyspnea control. Buspirone has no impact on dyspnea.⁵⁴ Although mirtazapine was found to reduce dyspnea, it was in a case series of six patients.⁵⁵ Benzodiazepines have been used in patients with severe dyspnea but a recent Cochrane review suggests that benzodiazepines do not improve dyspnea.⁵⁶ Instead, they may reduce anxiety which can be both a trigger for and a consequence of dyspnea. This must be weighed against the potential adverse effects of benzodiazepines, including an increased risk of mortality.⁵⁰

SUMMARY

Clinicians routinely care for patients struggling with chronic breathlessness. Inpatient and outpatient encounters are an opportunity to develop symptom-directed plans of care beyond the routine disease-targeting therapies typically prescribed. If patients remain breathless despite medical optimization, non-pharmacologic therapies and opioids can provide significant relief. By using a systematic approach to the management of dyspnea, internists can avoid missed opportunities to recognize this often life-changing symptom while ensuring that patients benefit from the gamut of evidence-based treatment options.

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Compliance with Ethical Standards:

Conflict of Interest: Neither author has any conflict of interest to report.

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