



REVIEW

Dyspnea in COPD: New Mechanistic Insights and Management Implications

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ABSTRACT

Dyspnea is the most common symptom experienced by patients with chronic obstructive pulmonary disease (COPD). To avoid exertional dyspnea, many patients adopt a sedentary lifestyle which predictably leads to extensive skeletal muscle deconditioning, social isolation, and its negative psychological sequelae. This “dyspnea spiral” is well documented and it is no surprise that alleviation of this distressing symptom has become a key objective highlighted across COPD guidelines. In reality, this important goal is often difficult to achieve, and successful symptom management awaits a

clearer understanding of the underlying mechanisms of dyspnea and how these can be therapeutically manipulated for the patients' benefit. Current theoretical constructs of the origins of activity-related dyspnea generally endorse the classical demand–capacity imbalance theory. Thus, it is believed that disruption of the normally harmonious relationship between inspiratory neural drive (IND) to breathe and the simultaneous dynamic response of the respiratory system fundamentally shapes the expression of respiratory discomfort in COPD. Sadly, the symptom of dyspnea cannot be eliminated in patients with advanced COPD with relatively fixed pathophysiological impairment. However, there is evidence that effective symptom palliation is possible for many. Interventions that reduce IND, without compromising alveolar ventilation (V_A), or that improve respiratory mechanics and muscle function, or that address the affective dimension, achieve measurable benefits. A common final pathway of dyspnea relief and improved exercise tolerance across the range of therapeutic interventions (bronchodilators, exercise training, ambulatory oxygen, inspiratory muscle training, and opiate medications) is reduced neuromechanical dissociation of the respiratory system. These interventions, singly and in combination, partially restore more harmonious matching of excessive IND to ventilatory output achieved. In this review we propose, on the basis of a

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thorough review of the recent literature, that effective dyspnea amelioration requires combined interventions and a structured multidisciplinary approach, carefully tailored to meet the specific needs of the individual.

Keywords: COPD; Dyspnea; Respiratory physiology

Key Summary Points

Dyspnea is the most common symptom in chronic obstructive pulmonary disease (COPD), resulting in significant morbidity and alleviating dyspnea is a key objective of COPD management

Dyspnea is believed to result from disruption of the normal relationship between inspiratory neural drive (IND) to breathe and the dynamic response of the respiratory system

Therapeutic interventions including bronchodilators, exercise training, ambulatory oxygen, inspiratory muscle training, and opiates can reduce dyspnea by reducing neuromechanical dissociation of the respiratory system

Dyspnea management is challenging, and effective management requires combined interventions and a multidisciplinary approach tailored to the individual patient

INTRODUCTION

Dyspnea is defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” and is the most common symptom in chronic obstructive pulmonary disease (COPD) [1]. Chronic dyspnea decreases engagement in physical activity and is associated with reduced health-related quality of life and increased

mortality [2, 3]. The mechanisms of dyspnea are complex and incompletely understood, and effective management of this distressing symptom is difficult. However, a personalized, patient-focused approach based on an understanding of the underlying mechanisms can yield meaningful benefits for many.

The overarching objectives of this review are (1) to consider current constructs of the neurophysiological mechanisms of activity-related breathlessness in patients with COPD, (2) to examine mechanisms of benefit of a variety of therapeutic interventions currently at our disposal, and (3) to review the evidence of the clinical efficacy of these treatments.

For the purpose of this review, the terms dyspnea, breathing discomfort, and breathlessness are used interchangeably. As a result of space constraints, the effects of endoscopic or surgical lung volume reduction and non-invasive mechanical ventilation are not discussed. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CURRENT CONSTRUCTS OF DYSPNEA CAUSATION

Quoting the renowned Canadian physiologist Norman Jones [4]: “breathlessness can be seen to result from the imbalance between the demand for breathing and the ability to achieve the demand.” Accordingly, breathlessness is invariable when there is a mismatch between increased inspiratory neural drive (IND) and an inadequate mechanical response of the respiratory system. This general “imbalance” concept is intuitively appealing and widely supported. This phenomenon has variously been termed demand–capacity imbalance, efferent–afferent dissociation, neuromuscular or neuromechanical dissociation.

Normally in health, unpleasant respiratory sensation is avoided as spontaneous breathing is unimpeded and neuromechanical harmony of the respiratory system is intact [5]. However, unpleasant respiratory sensation can be provoked in healthy volunteers during

experimental chemical and respiratory mechanical loading [6–10]. For example, when spontaneous tidal volume (V_T) expansion is constrained in the face of increased or persistent chemostimulation, unpleasant respiratory sensations (e.g., “sense of air hunger”) are consistently perceived [11]. The same is true of young healthy subjects during exercise: combined chemical (added 0.6 L dead space, equivalent to CO_2 rebreathing) and external mechanical loading (chest wall strapping to constrain V_T expansion) amplified intensity of breathing discomfort and exercise intolerance to a much greater extent than either intervention in isolation [12].

NEUROPHYSIOLOGY OF DYSPNEA

Briefly, information on the amplitude of motor command output from respiratory control centers in the medulla and cerebral cortex is relayed to the somatosensory cortex via central corollary discharge or efferent copy (Fig. 1) [13–15]. Direct chemostimulation of medullary-pontine centers is immediately associated with perceived severe breathing difficulty in healthy volunteers, even in the absence of any respiratory muscle activity [16]. It is believed that increased motor command output from cortical motor centers, in response to experimentally increased inspiratory muscle impedance or weakness, is consciously perceived as increased perceived respiratory effort [6, 16]. During

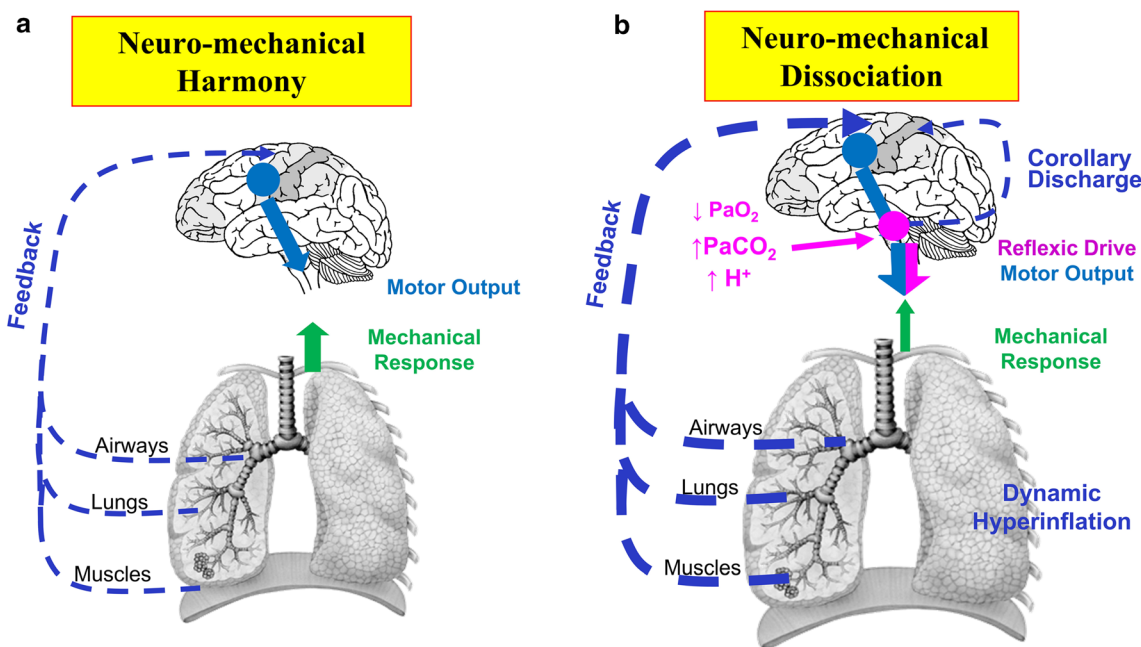


Fig. 1 **a** Neuromechanical harmony and **b** dissociation in a patient with COPD during exertion. **a** Synchronous activation of the respiratory and locomotor muscles with progressive motor command output increases to maintain ventilation with activity initiation. **b** Arterial oxygen desaturation, increased $[H^+]$, and increased VCO_2 with corresponding chemostimulation of medullary centers and increased IND as exercise continues. Resting and dynamic hyperinflation and resulting mechanical constraints lead to neuromechanical dissociation and distressing unsatisfied

inspiration during exertion. *COPD* chronic obstructive pulmonary disease, $[H^+]$ hydrogen ion concentration, *IND* inspiratory neural drive, $PaCO_2$ arterial partial pressure of carbon dioxide, PaO_2 arterial partial pressure of oxygen, VCO_2 carbon dioxide production. Reprinted from Clin Chest Med, 40(2): Denis E. O’Donnell, Matthew D. James, Kathryn M. Milne, J. Alberto Neder, The pathophysiology of dyspnea and exercise intolerance in chronic obstructive pulmonary disease, 343–366, Copyright (2019), with permission from Elsevier

external mechanical loading, diverse afferent inputs from sensory receptors throughout the respiratory system are altered or disrupted and this information is conveyed to respiratory control centers and the somatosensory cortex. The collective sensory information from both central (brain) and peripheral (respiratory system) sources is centrally integrated and the net effect of efferent–afferent dissociation results in conscious perception of unpleasant respiratory sensations, e.g., unsatisfied inspiration [13–15].

Beyond a certain threshold, escalating breathing difficulty is experienced as an imminent threat to life or well-being, demanding immediate behavioral action [17]. Recent studies using functional magnetic resonance imaging (fMRI) of the brain have shown that when neuromechanical dissociation is experimentally induced by uncoupling of chemical stimulus and mechanical response, there is increased activation of limbic and paralimbic centers which, combined with sympathetic nervous system overactivation, results in anxiety, panic, and affective distress [18].

EXERTIONAL DYSPNEA IN COPD

The demand–capacity imbalance theory is supported by a number of studies which show strong statistical correlations between the rise in dyspnea intensity during exercise and simultaneous increase in a number of physiological ratios which ultimately reflect increased neuromechanical disruption (Table 1). Collectively, these data support the notion that dyspnea increases as a function of increasing IND (from bulbo-pontine and cortical respiratory control centers) in the face of an ever-decreasing capacity of the respiratory system to respond.

Increased Inspiratory Neural Drive

Diaphragm electromyography (EMGdi), measured using an esophageal catheter with multiple paired electrodes, generally gives a more accurate assessment of IND (EMGdi/EMGdi,max) than minute ventilation (V_E) or esophageal pressures which are strongly influenced by

Table 1 Physiologic ratios highly correlated with increasing dyspnea throughout exercise

Physiologic ratio	Response during exercise and significance
V_E/MVC [103, 104]	Ventilation increasing to maximum capacity
$Pes/Pes,max$ [6, 105]	Respiratory effort approaches maximum volitional value
V_T/IC [88, 89, 106]	Mechanical constraints on tidal volume become critical
EMGdi/ EMGdi,max [19, 20]	Tidal IND to the diaphragm approaches maximum volitional value

EMGdi diaphragmatic electromyography, *EMGdi/EMGdi,max* inspiratory neural drive, *IC* inspiratory capacity, *IND* inspiratory neural drive, *MVC* maximum ventilatory capacity, *Pes* esophageal pressure, *Pes,max* maximum esophageal pressure, V_T tidal volume, V_E minute ventilation

the prevailing dynamic mechanical constraints in COPD [19–23]. During cycle ergometry in patients with COPD (compared with age- and sex-matched healthy controls), EMGdi/EMGdi,max is increased at rest and at any given level of oxygen consumption (VO_2) and V_E [24–26]. The slope of diaphragmatic activation versus work rate becomes steeper as pulmonary gas exchange and mechanical abnormalities worsen with COPD disease progression (Fig. 2) [24–26]. Remarkably, one recent study showed that the dyspnea-EMGdi/EMGdi,max slope is similar in subjects with COPD and those with interstitial lung disease (ILD) who have a similar resting inspiratory capacity (IC) reduction. This relationship held despite marked intergroup differences in lung compliance, breathing pattern, operating lung volumes, respiratory muscle recruitment pattern, and pulmonary gas exchange abnormalities [24]. Thus, dyspnea intensity/IND slopes were constant in these two diverse conditions despite vast differences in the source and type of afferent sensory inputs to the brain.

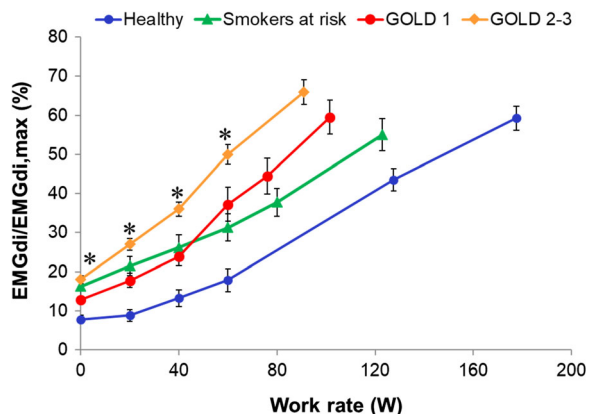


Fig. 2 Inspiratory neural drive during exercise represented by diaphragmatic activation as a percentage of maximal diaphragmatic activation (EMGdi/EMGdi,max) across healthy controls, smokers, and spectrum of COPD. Values are mean ± SEM. **p* < 0.05 significantly different from healthy controls at a given work rate. COPD chronic obstructive pulmonary disease, EMGdi/EMGdi,max index of inspiratory neural drive to the crural diaphragm, GOLD Global Initiative for Chronic Obstructive Lung Disease, SEM standard error of the mean. Adapted from Guenette JA, et al. Mechanisms of exercise intolerance in Global Initiative for Chronic Obstructive Lung Disease grade 1 COPD. *Eur Respir J.* 2014;44(5):1177–1187. Adapted from Elbehairy AF, et al. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J.* 2016;48(3):694–705. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, Neder JA, O'Donnell DE. 2016. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med.* 193(3):299–309. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society

Mechanisms of Increased Inspiratory Neural Drive in COPD

Pulmonary Gas Exchange Abnormalities and Acid–Base Imbalance

The causes of increased IND during exercise in COPD include chemical and mechanical factors (Table 2) [19, 20, 24–26]. In both healthy controls and subjects with COPD, IND increases as

Table 2 Stimulus for increased inspiratory neural drive to the diaphragm

Chemical	Mechanical	Other
Increased VCO ₂ :	Increased respiratory muscle loading/ weakness	Altered cardiovascular afferent activity
Increased physiologic dead space		Increased sympathetic system activation
Early metabolic acidosis		
Increased work of breathing		
Hypoxemia		
Ergoreceptor activation		

VCO₂ carbon dioxide production

metabolic carbon dioxide output (VCO₂) increases during exercise. Thus, exercise hyperpnea is very closely linked to pulmonary CO₂ gas exchange. In COPD, ventilation–perfusion mismatch in the lung leads to inefficient pulmonary gas exchange. Dysfunction of the lung microvasculature occurs to a variable extent across the entire severity spectrum of COPD [27–29]. In mild COPD during exercise, physiological dead space, the ventilatory equivalent for CO₂ (V_E/VCO₂)—a measure of ventilatory efficiency—and alveolar ventilation (V_A) are all elevated, compared with healthy controls [27]. It is now clear that these high ventilatory requirements when combined with expiratory flow limitation (EFL) lead to worsening dynamic mechanics and earlier exercise cessation [27, 30, 31]. Additionally, the associated tachypnea and shallow breathing during exercise further increase dead space to tidal volume ratio (V_D/V_T) [28].

Critical arterial hypoxemia (< 60 mmHg) due to the presence of lung units with low ventilation–perfusion ratios combined with low

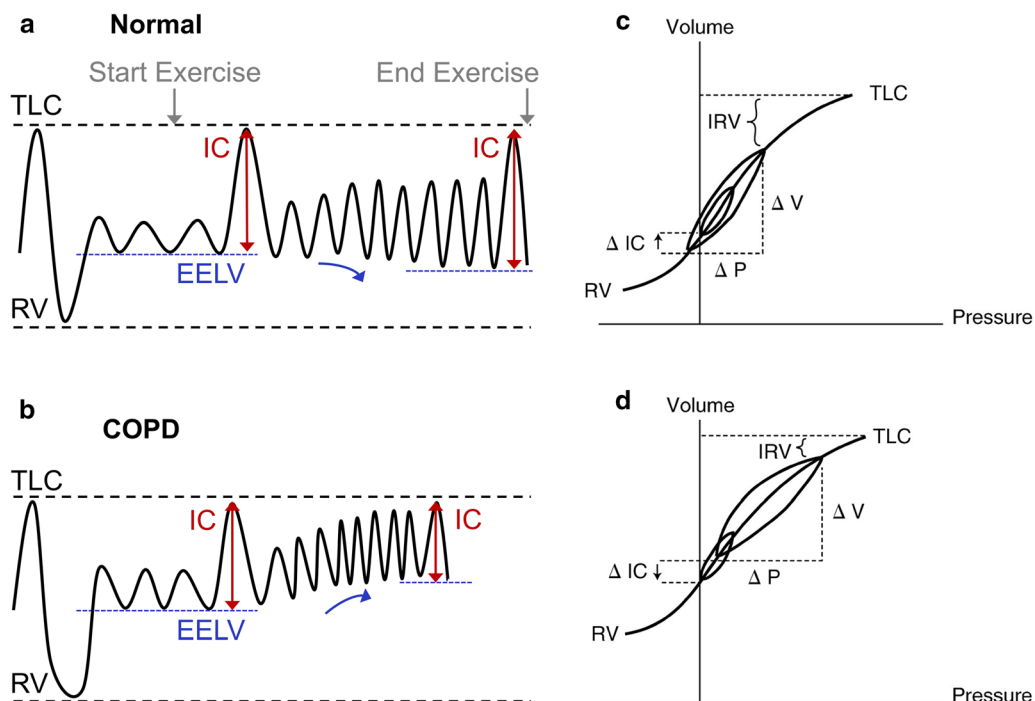


Fig. 3 Change in EELV, IC, and IRV during exercise in **a** normal lungs and **b** COPD demonstrating change in position of V_T relative to TLC on pressure–volume curve (**c, d**) of the respiratory system. *COPD* chronic obstructive pulmonary disease, *EELV* end-expiratory lung volume, *IC* inspiratory capacity, *IRV* inspiratory reserve volume, *RV* residual volume, *TLC* total lung capacity, V_T tidal volume.

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mixed venous O_2 will stimulate peripheral and central chemoreceptors and further increase IND [32–35]. The rate of rise of IND during exercise is also strongly influenced by augmented chemosensitivity as manifested by a lower partial pressure of arterial CO_2 ($PaCO_2$) at rest. The respiratory control centers adjust to maintain $PaCO_2$ within a narrow range during rest and exercise: the lower the resting $PaCO_2$ level, the higher the IND, V_A , and V_E during exercise [35, 36]. The co-existence of increased chemosensitivity and high physiological dead space greatly augments IND and associated dyspnea.

In COPD, skeletal muscle deconditioning (reduced oxidative capacity) manifests as metabolic acidosis at relatively low VO_2 (low anaerobic threshold)—an additional powerful ventilatory stimulus [37–41]. Exercise

hyperpnea is also provoked by ascending sensory inputs from thinly myelinated (type III and IV) afferents in the active locomotor muscles [34] responding to mechanical distortion and metabolite accumulation during exercise [42].

Dynamic Respiratory Mechanics

While expiratory flow limitation (EFL) is the hallmark of COPD, associated lung hyperinflation has important negative sensory consequences [43]. Emphysematous destruction of the lungs' connective tissue matrix leads to increased lung compliance and this resets the balance of forces between inward lung recoil pressure and outward chest wall recoil at end-expiration. As a result, the relaxation volume of the respiratory system (i.e., end-expiratory lung volume, EELV) is increased compared with healthy controls (Fig. 3). In patients with EFL,

EELV is also dynamically determined and is a continuous variable that is influenced by the prevailing breathing pattern. If breathing frequency (Bf) increases abruptly (and expiratory time decreases and/or V_T increases) in patients with significant EFL, air trapping is inevitable, given the slow mechanical time-constant for lung emptying in COPD. Thus, during exercise, EELV increases temporarily and variably above its resting value: this is termed dynamic lung hyperinflation [44–50].

The resting IC and inspiratory reserve volume (IRV) indicate the operating position of V_T relative to total lung capacity (TLC) and the upper curvilinear portion of the relaxed respiratory system S-shaped pressure–volume relationship (Fig. 3). Breathing close to TLC means that the inspiratory muscles are foreshortened, functionally weakened, and must contend with increased elastic and inspiratory threshold loading (to overcome auto-positive end-expiratory pressure, PEEP). The difference between end-inspiratory lung volume (EILV) and TLC (i.e., the size of the IRV) largely dictates the relationship between IND and the mechanical/muscular response of the respiratory system and hence the degree of dyspnea experienced throughout exercise. In other words, the dynamic decrease in IRV provides crucial information about the extent of neuromechanical dissociation of the respiratory system and correlates strongly with dyspnea intensity ratings. The smaller the resting IC and IRV (the greater the increase in resting EELV), the shorter the time during exercise before V_T reaches an inflection or plateau and dyspnea abruptly escalates. Thus, when the V_T/IC ratio reaches approximately 0.7 during exercise, a widening disparity occurs between IND and the V_T response [51]. IND continues to rise and V_T expansion becomes progressively constrained and eventually fixed, representing the onset of severe neuromechanical dissociation [43]. At this point the qualitative descriptor “increased breathing effort” is displaced by “unsatisfied inspiration” as the dominant descriptor of dyspnea [52].

Dynamic hyperinflation results in a relatively rapid and shallow breathing pattern: the attendant increased velocity of shortening of

the inspiratory muscles results in functional muscle weakness, decreases dynamic lung compliance, worsening pulmonary gas exchange (higher V_D/V_T) and negative cardiopulmonary interactions (reduced venous return and reduced left ventricular ejection fraction) [53–56]. With increasing mechanical impairment and progressive resting lung hyperinflation as COPD progresses, these abnormal physiological events appear at progressively lower exercise intensities.

IMPROVING INSPIRATORY NEURAL DRIVE

Can We Reduce Inspiratory Neural Drive?

Unfortunately, high physiological dead space is virtually immutable in COPD especially when the cause is emphysematous destruction of the pulmonary vascular bed. First-line dyspnea-relieving therapies such as bronchodilators, which reduce regional lung hyperinflation and improve breathing pattern, result in only small increases in V_A and V_E with essentially no change in dead space ventilation, at least in mild to moderate COPD [57]. In more advanced COPD, modest increases in pulmonary blood flow can occur following bronchodilators and endoscopic lung volume reduction [58, 59]. Inhaled or oral vasodilator therapy also has the potential to improve pulmonary blood flow in selected patients with COPD [60]. However, the overall sensory benefits of improving regional pulmonary blood flow will depend on the net effect on ventilation–perfusion matching and in particular the degree of attenuation of wasted ventilation and reduction of IND. A summary of the interventions for dyspnea management reviewed below is presented in Table 3.

Supplemental Oxygen

Hyperoxia inhibits carotid chemoreceptor stimulation of V_E during exercise by reducing Bf, resulting in a reduction in V_E by approximately 3–6 L/min (Fig. 4) [61]. Additionally, improved O_2 delivery to the active locomotor

Table 3 Summary of therapeutic interventions, respective mechanisms, and examples of previously studied therapies for dyspnea alleviation in COPD

Goal	Therapy	Mechanism	Example of use
Reduce IND	O ₂ ^a	Inhibition of carotid chemoreceptor stimulation Delay lactate accumulation ↓DH (achieved by ↓Bf)	Selection of oxygen delivery system, device, and flow rate must be tailored to the patient to best support mobility and quality of life [107]. Delivery system options include: Liquid oxygen Stationary or portable oxygen concentrator Compressed gas cylinders Device options include: Nasal cannula Simple mask Reservoir nasal cannula
	Opiates	Alteration of central processing of dyspnea-stimulating afferent signals	Initial dose and titration of opioids must be personalized with monitoring for adverse effects. Previously studied opioids in COPD: Orally administered morphine (both immediate release and sustained release) dose range 5 mg to 40 mg [72]
Improve respiratory mechanics	Bronchodilators	↓DH (improve airway conductance and ↓time constant, ↑IC and delay critical ↓IRV) ↓Mechanical loading (↓elastic and inspiratory threshold loads) and ↑functional inspiratory muscle strength	Previously studied LABA/LAMA combinations [90, 92]: Tiotropium–olodaterol 5–5 µg inhaled daily Umeclidinium bromide–vilanterol 62.5–25 µg inhaled daily
	IMT ^b	↑Functional inspiratory muscle strength at given V _E and operating lung volumes	Previously studied IMT [96]: 30 breaths (4–5 min sessions) twice to three times daily using handheld POWERbreathe KH2 device for 8 weeks

Table 3 continued

Goal	Therapy	Mechanism	Example of use
Combined	Exercise training	<p>↓Lactate production, VCO_2, V_E at given exercise intensity</p> <p>↓DH (achieved by ↓Bf)</p>	<p>Previously studied exercise training programs:</p> <p>High intensity (90% of the AT work rate) exercise for 5 days/week for 8 weeks [37]</p> <p>Interval training (100% peak work rate for 30 s alternating with 30 s unloaded pedaling) for 40 min/day, 2 days/week for 12 weeks [108]</p> <p>General exercise training program including cycle exercise and resistance training 3 days/week for 6 weeks [109]</p> <p>Pulmonary rehabilitation should include [85, 110]:</p> <p>Exercise training (endurance or interval training and resistance training)</p> <p>Education</p> <p>Psychosocial support</p> <p>Minimum 8 weeks duration</p> <p>Can occur in the inpatient or outpatient setting</p>

AT anaerobic threshold, *Bf* breathing frequency, *COPD* chronic obstructive pulmonary disease, *DH* dynamic hyperinflation, *IC* inspiratory capacity, *IMT* inspiratory muscle training, *IND* inspiratory neural drive, *IRV* inspiratory reserve volume, *LABA* long-acting beta-2 agonist, *LAMA* long-acting muscarinic antagonist, *PI_{max}* maximum inspiratory pressure

^a Survival benefit demonstrated in subjects with resting $PaO_2 \leq 55$ mmHg or $PaO_2 < 60$ mmHg with cor pulmonale, right heart failure, or erythrocytosis [64, 65]. Qualification for long-term domiciliary oxygen varies by jurisdiction

^b In patients with COPD and inspiratory muscle weakness defined as $PI_{max} < 70$ cmH₂O [96]

muscles delays lactate accumulation (hydrogen ion stimulation), and likely alters afferent inputs from peripheral muscle ergoreceptors. The effects of O₂ on IND and V_E are more pronounced in patients with significant baseline arterial hypoxemia but some individuals with milder exercise arterial O₂ desaturation can also benefit [33, 61–63]. Other established benefits of supplemental O₂ include reduced dynamic hyperinflation secondary to reduced Bf, improved cardiocirculatory function (e.g., reduced pulmonary artery resistance), and delayed skeletal muscle fatigue [34]. The relative contribution of these altered physiological

responses to dyspnea relief during exercise will vary across individuals.

Landmark clinical trials assessing the use of oxygen therapy in COPD have demonstrated the mortality benefit of continuous ambulatory oxygen in patients with significant hypoxemia [64, 65]. A recent systematic review examined 44 studies that assessed the impact of supplemental ambulatory oxygen on symptoms in patients with COPD who did not qualify for supplemental oxygen on the basis of thresholds from landmark studies (mean $PaO_2 > 55$ mmHg). Oxygen supplementation reduced dyspnea in patients undergoing

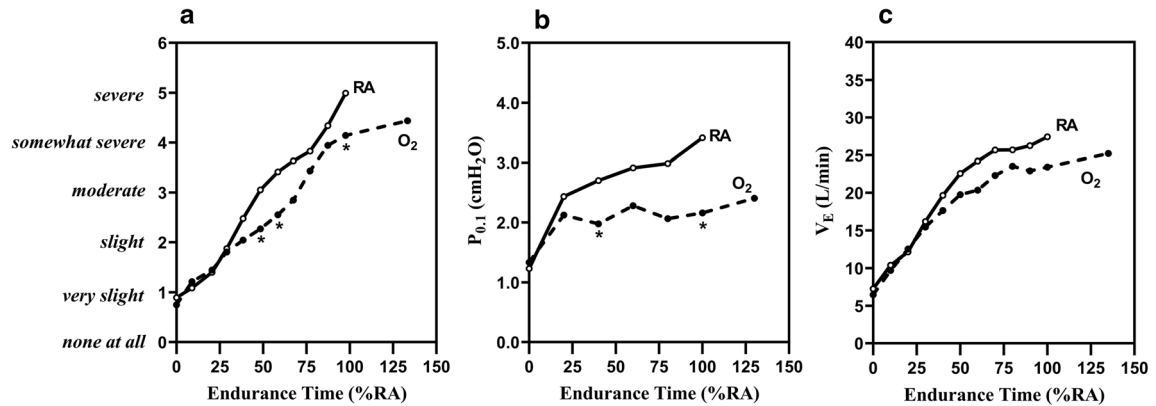


Fig. 4 Improvement in **a** dyspnea, **b** $P_{0.1}$ (a surrogate measure of inspiratory neural drive), and **c** V_E with administration of oxygen in patients with moderate to severe COPD and mild exertional oxygen desaturation, not qualifying for ambulatory home oxygen. RA room air, $P_{0.1}$ airway occlusion pressure, V_E minute ventilation. Reprinted with permission of the American Thoracic Society.

Copyright © 2019 American Thoracic Society. O'Donnell DE, Bain DJ, Webb KA. 1997. Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. *Am J Respir Crit Care Med.* 155(2):530–535. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society

cardiopulmonary exercise testing compared to patients exercising without oxygen; however, evidence of an effect on daily activities was limited [63–65].

Opiates

Respiratory depression is a well-recognized complication of opioid therapy in susceptible older patients with more advanced COPD [66–72]. In clinically stable patients with COPD, careful upward titration of opiate medication is generally safe in selected patients. Abdallah et al. [73] have recently shown that a single dose of fast-acting, orally administered morphine in patients with COPD was associated with improvements in dyspnea and exercise endurance but with considerable variation in response [73]. Of interest, this subjective improvement occurred in the absence of significant decreases in IND (EMGdi/EMGdi,max), Bf, and V_E . The authors speculated that opiates may alter the central processing of sensory signaling related to dyspnea and may influence the affective dimension by acting on abundant opioid receptors in cortico-limbic centers of the brain.

Although opioids are recommended for dyspnea management in patients with chronic

lung disease [1], a recent systematic review of 26 studies that investigated the role of various opiates for palliation of refractory breathlessness in advanced disease determined that opiates provided a minor improvement in breathlessness scores compared to placebo (– 3.36 from baseline on 100 mm visual analog scale [VAS]; minimal clinically important difference [MCID] – 9) [74]. These studies, which included patients with refractory breathlessness despite optimal medical management, provided weak evidence for oral and parenteral administration of opiates, and no evidence for nebulized administration [74]. A recently published randomized controlled trial (RCT) evaluating the impact of regular sustained-release orally administered morphine for chronic breathlessness (modified Medical Research Council [mMRC] ≥ 2) in patients with a range of diagnoses, including COPD, found no difference in dyspnea severity reduction between orally administered morphine and placebo arms of the study [75]. However, subjects in the morphine arm used less as needed rescue immediate release orally administered morphine [75].

Exercise Training

In one important study, a high intensity exercise training (EXT) program was associated with consistent physiological training effects such as reduced lactic acid, VCO_2 , and V_E at a given exercise intensity (Fig. 5) [37]. Such improvements in acid–base status likely reduce IND and dyspnea by altering central and peripheral chemoreceptor activation, in part reflecting altered activation patterns of locomotor muscle ergoreceptors. The associated reduced Bf has been shown to reduce dynamic hyperinflation

with consequent delay of intolerable dyspnea [76–79]. However, it is now clear that important improvements in activity-related dyspnea, quality of life, and perceived self-efficacy can occur in the absence of consistent physiological training effects in patients with more advanced COPD [80]. Thus, supervised multicomponent, pulmonary rehabilitation programs appear to positively modify behavior and address the important affective component of dyspnea [81]. This is corroborated by a recent study which demonstrated that pulmonary rehabilitation in COPD consistently altered brain activity in

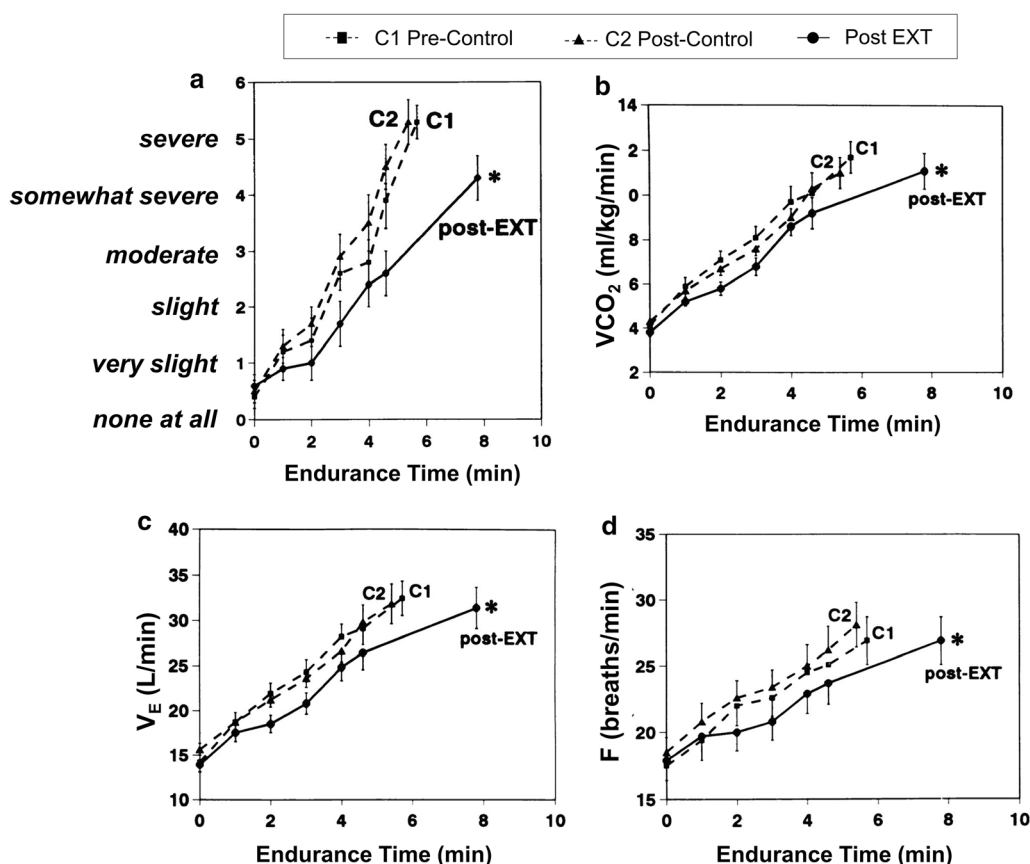


Fig. 5 Reduced a exertional breathlessness during constant-load cycle exercise after exercise training (EXT) or control intervention in patients with COPD. Slopes of b carbon dioxide output (VCO_2), c ventilation (V_E), and d breathing frequency also fell significantly after EXT. * $p < 0.05$. COPD chronic obstructive pulmonary disease, EXT exercise training, F breathing frequency, VCO_2 carbon dioxide production, V_E minute ventilation, V_T tidal volume. Reprinted with permission of the American

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stimulus valuation networks, measured by brain fMRI [82]. A systematic review of 65 RCTs of pulmonary rehabilitation programs demonstrated significant improvement in dyspnea and pulmonary rehabilitation is recommended in international guidelines for patients with COPD and persistent dyspnea [83–85]. It was noted that these programs enhanced the patients' sense of control over their condition and significantly improved health-related quality of life [83].

IMPROVING VENTILATORY CAPACITY: RESPIRATORY MECHANICS AND MUSCLE FUNCTION

Reducing Lung Hyperinflation

Bronchodilators improve airway conductance and shorten the time constant for lung emptying. In this way, they reduce lung hyperinflation [86]. The resultant increase in IC and IRV allows greater V_T expansion and higher V_E during exercise with a delay in reaching critical mechanical limits where dyspnea becomes intolerable [30]. Increased IC at rest and during exercise means that V_T occupies a lower position on the sigmoidal pressure–volume curve of the relaxed respiratory system (Fig. 6). Thus, the

net effect is reduced intrinsic mechanical loading (i.e., elastic and inspiratory threshold loads) and increased functional strength of the inspiratory muscles. Ultimately, lung deflation partially restores a more harmonious relationship between IND and V_T displacement: less effort is now required for a given or greater V_T (Fig. 6) [87–89].

The superiority of dual combined long-acting beta-2 agonist and muscarinic antagonist (LABA/LAMA) bronchodilators relative to the individual mono-components is modest at best [90, 91]. A systematic review of 99 RCTs indicates that while dual long-acting bronchodilators often reduce dyspnea, increase lung function (improved forced expiratory volume in 1 s, FEV₁), and improve quality of life compared to single long-acting bronchodilators or LABA/inhaled corticosteroid (ICS) combinations [92], these results are not consistent and vary in magnitude. Current guidelines recommend LABA/LAMA combination therapy for patients whose symptoms are not controlled by a single long-acting bronchodilator [84, 93–95].

Inspiratory Muscle Training (IMT)

In a recent study Langer et al. [96] showed that supervised IMT in patients with severe COPD and baseline inspiratory muscle weakness was associated with increased inspiratory muscle

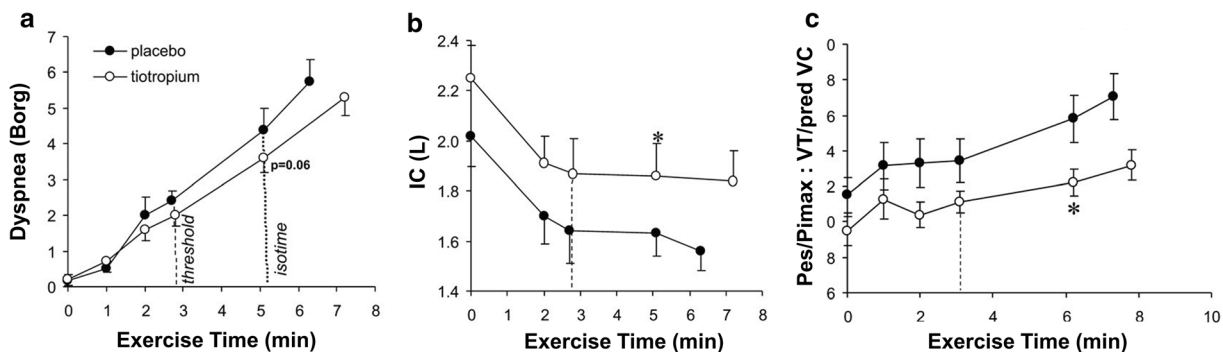


Fig. 6 Ventilatory responses to CWR exercise between tiotropium and placebo demonstrating reduced **b** dynamic hyperinflation with **c** improved musculo-mechanical coupling and **a** reduced dyspnea. CWR constant work rate, IC inspiratory capacity, $Pes/P_{I_{max}}$ tidal esophageal pressure

relative the maximum esophageal inspiratory pressure, V_T tidal volume. Adapted from O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. J Appl Physiol. 2006;101(4):1025–1035

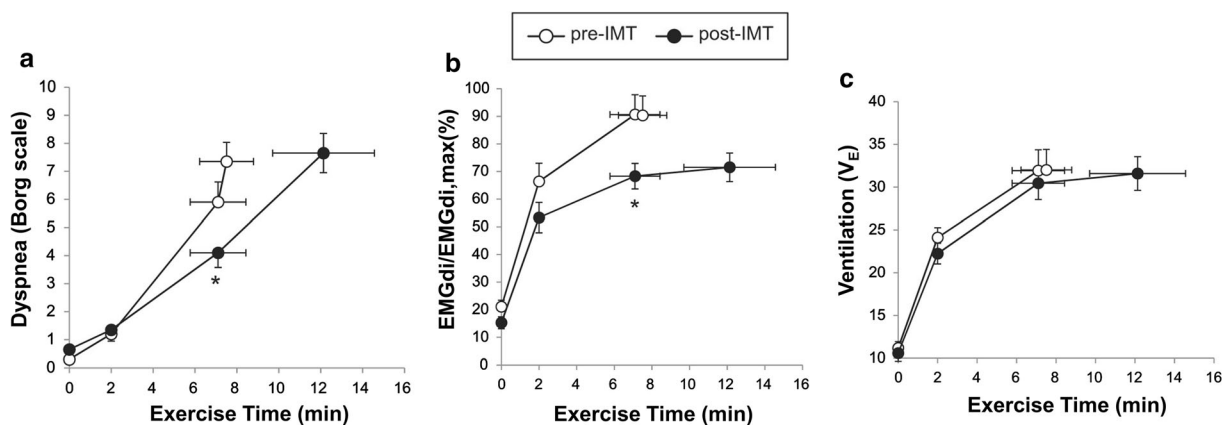


Fig. 7 Improvement in **a** dyspnea, **b** inspiratory neural drive ($EMG_{di}/EMG_{di,max}$), and **c** ventilation following IMT in patients with COPD and evidence of inspiratory muscle weakness. COPD chronic obstructive pulmonary disease, $EMG_{di}/EMG_{di,max}$ index of inspiratory neural drive to the crural diaphragm, IMT inspiratory muscle

training, V_E minute ventilation. Adapted from Langer D, Ciavaglia C, Faisal A, Webb KA, Neder JA, Gosselink R, Dacha S, Topalovic M, Ivanova A, O'Donnell DE. Inspiratory muscle training reduces diaphragm activation and dyspnea during exercise in COPD. *J Appl Physiol.* 2018;125(2):381–392

strength, reduced dyspnea, and improved exercise tolerance compared with sham training (Fig. 7). In the active IMT group, IND fell significantly over the increased exercise endurance time (> 3 min) during which V_E was sustained at approximately 30 L/min (Fig. 7). Of interest, IND ($EMG_{di}/EMG_{di,max}$) was diminished after IMT in a setting of no change in V_E , breathing pattern, or operating lung volumes. This study, therefore, supports the notion that when the inspiratory muscles are weakened in COPD, the rise in IND during exercise reflects increasing motor command output from cortical centers in the brain to maintain force generation commensurate with the ventilatory demand. The increased IND under these conditions contributed to exertional dyspnea: reduced IND and dyspnea as muscle function improved supports this contention.

A meta-analysis of 32 RCTs on the effects of IMT in patients with COPD spanning all disease severities showed that IMT led to a significant reduction in dyspnea (Borg score – 0.9 units; TDI + 2.8 units) compared to patients without IMT [97]. A systematic review of studies that evaluated the utility of IMT in patients with COPD showed that IMT reduces symptoms of dyspnea (Borg scale – 0.52 units difference, IMT vs. control; baseline and transition dyspnea

index [BDI-TDI]: 2.30 units difference, IMT vs. control). The minimal clinically important difference for TDI is 1 unit [98]. There was no benefit of adjunctive IMT in patients completing a pulmonary rehabilitation program [99].

CHALLENGES OF DYSPNEA MANAGEMENT IN COPD

Effective dyspnea management for patients with COPD presents an important challenge requiring comprehensive clinical history taking and a basic understanding of the neurophysiological mechanisms of dyspnea as discussed. Multiple contributory factors often exist and need to be identified and treated to optimize individual management. These include negative effects of obesity or malnutrition, anxiety and depression, and impairment in cardiocirculatory and musculoskeletal function. The symptom of dyspnea is a uniquely personal experience and difficult to quantify numerically with magnitude-of-tasks questionnaires (mMRC) or even multicomponent questionnaires which evaluate intensity, quality, affective dimension, and impact on quality of life (BDI-TDI) [98, 100, 101].

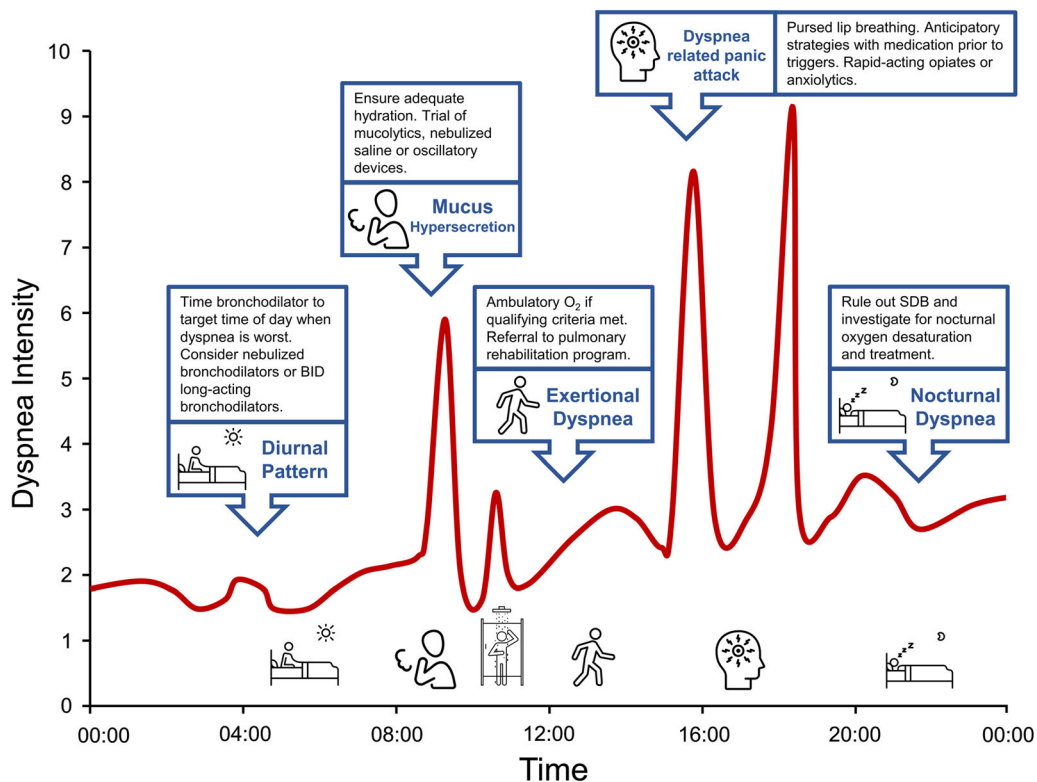


Fig. 8 Individual dyspnea intensity profile of a patient with COPD and highlighted management interventions targeting dyspnea triggers and underlying physiological

mechanisms. *BID* twice daily, *COPD* chronic obstructive pulmonary disease, *SDB* sleep disordered breathing. Icons presented in the figure from the Noun Project

Patients with COPD may present with very different individual dyspnea profiles (Fig. 8). Some patients experience increased nighttime and early morning dyspnea. Distressing dyspnea is often provoked by bouts of coughing and difficult sputum expectoration. Dyspnea may be predominantly associated with physical activity or be characterized by a gradual increase in intensity and fatigue throughout the day, punctuated by episodes of “breakthrough” dyspnea or crisis. Each scenario requires a personalized approach to management that ideally is tailored to the individual’s dyspnea profile.

According to most current recommendations [1], the first step in alleviating dyspnea in COPD is to optimize bronchodilator therapy to improve respiratory mechanics and muscle function, thus increasing exercise capacity. The second step is to promote regular physical activity or, if at all possible, to enroll the patient in a supervised, multidisciplinary pulmonary

rehabilitation program. A recent study has demonstrated that patients with moderate to severe chronic activity-related breathlessness are not referred to pulmonary rehabilitation programs despite evidence that these patients derive benefit [102]. Potential additional benefits of pulmonary rehabilitation include improved peripheral muscle function and acid–base balance with reduced IND and secondary improvements in dynamic respiratory mechanics and muscle function. Individualized inspiratory muscle training may benefit some patients with advanced COPD who have objective inspiratory muscle weakness. For selected individuals with severe dyspnea and significant arterial O_2 desaturation during ($SpO_2 < 88\% O_2$ for more than two consecutive minutes) a weight-bearing endurance test, a trial of ambulatory O_2 treatment should be considered to facilitate increased physical activity. Opiates are generally reserved for patients with

incapacitating dyspnea and need to be carefully supervised.

Taken together, the majority of clinical trials on efficacy of common treatment interventions report only minor gains in dyspnea alleviation compared with placebo. This reflects the vast pathophysiological heterogeneity of COPD with consequent variability in response patterns to any single intervention. Many dyspnea assessment instruments, currently at our disposal, lack the sensitivity to measure the longitudinal impact of single or combined interventions on the daily burden of dyspnea. It must be emphasized that multidisciplinary management is generally required for refractory dyspnea and this should be tailored to the specific needs of the individual, determined by careful evaluation. Thus, refinements in evaluation of patterns of precipitation of dyspnea and individual daily profiles might offer greater precision in the future development of more effective symptom management.

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