

Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guideline

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Dyspnea is a cardinal symptom of chronic obstructive pulmonary disease (COPD), and its severity and magnitude increases as the disease progresses, leading to significant disability and a negative effect on quality of life. Refractory dyspnea is a common and difficult symptom to treat in patients with advanced COPD. There are many questions concerning optimal management and, specifically, whether various therapies are effective in this setting. The present document was compiled to address these important clinical issues using an evidence-based systematic review process led by a representative interprofessional panel of experts.

The evidence supports the benefits of oral opioids, neuromuscular electrical stimulation, chest wall vibration, walking aids and pursed-lip breathing in the management of dyspnea in the individual patient with advanced COPD. Oxygen is recommended for COPD patients with resting hypoxemia, but its use for the targeted management of dyspnea in this setting should be reserved for patients who receive symptomatic benefit. There is insufficient evidence to support the routine use of anxiolytic medications, nebulized opioids, acupuncture, acupressure, distractive auditory stimuli (music), relaxation, handheld fans, counselling programs or psychotherapy. There is also no evidence to support the use of supplemental oxygen to reduce dyspnea in nonhypoxemic patients with advanced COPD.

Recognizing the current unfamiliarity with prescribing and dosing of opioid therapy in this setting, a potential approach for their use is illustrated. The role of opioid and other effective therapies in the comprehensive management of refractory dyspnea in patients with advanced COPD is discussed.

Key Words: *Chronic obstructive pulmonary disease; COPD; Dyspnea; Management*

Dyspnea is the subjective experience – usually unpleasant – of discomfort with breathing (1). Dyspnea is a cardinal symptom of chronic obstructive pulmonary disease (COPD), and its severity and magnitude increases as the underlying disease progresses, leading to significant disability. For patients with advanced COPD, dyspnea profoundly affects quality of life (QoL) to the extent that patients become isolated, often describing themselves as ‘existing’ rather than ‘living’ (1). Patients with advanced COPD almost universally experience significant dyspnea in the final year of life (2). Moreover, COPD patients at the end of life experience more dyspnea than lung cancer patients (2) and, yet, are often prescribed less medication and have less access to comprehensive care than patients dying from lung cancer (3,4).

La prise en charge de la dyspnée chez les patients atteints de maladie pulmonaire obstructive chronique avancée : des directives cliniques de la Société canadienne de thoracologie

La dyspnée est un symptôme cardinal de maladie pulmonaire obstructive chronique (MPOC). Sa gravité et son importance s'accroissent à mesure que progresse la maladie, entraînant une invalidité marquée et un effet négatif sur la qualité de vie. La dyspnée réfractaire est un symptôme courant et difficile à traiter chez les patients atteints de MPOC avancée. De nombreuses questions se posent quant à sa prise en charge optimale, notamment si diverses thérapies sont efficaces dans un tel contexte. Le présent document a été compilé pour répondre à ces questions cliniques importantes au moyen d'un processus systématique probant dirigé par un groupe représentatif d'experts interprofessionnels.

Les données probantes appuient les bienfaits des opioïdes par voie orale, de la stimulation neuromusculaire électrique, de la vibration de la paroi de la cage thoracique, des aides à la marche et de la respiration les lèvres pincées pour prendre en charge la dyspnée chez un patient ayant une MPOC avancée. L'oxygène est recommandé chez les patients atteints de MPOC qui font de l'hypoxémie au repos, mais son utilisation pour la prise en charge ciblée de la dyspnée devrait être réservée aux patients qui en tirent des bienfaits symptomatiques. On ne possède pas assez de données probantes pour étayer l'utilisation systématique des anxiolytiques, des opioïdes par nébulisation, de l'acupuncture, de l'acupression, du stimulus sonore distrayant (musique), de la relaxation, des éventails, des programmes de counseling ou de la psychothérapie. Par ailleurs, on ne possède pas de données probantes pour appuyer l'utilisation de suppléments d'oxygène pour réduire la dyspnée chez les patients non hypoxémiques ayant une MPOC avancée.

Compte tenu du peu de connaissances actuelles sur la prescription et la posologie des traitements aux opioïdes dans cette situation, on expose une démarche potentielle relativement à leur utilisation. Le rôle des opioïdes et d'autres thérapies efficaces pour la prise en charge complète de la dyspnée réfractaire chez les patients ayant une MPOC avancée est présenté.

The prevention, relief, reduction and soothing of dyspnea symptoms – without affecting a cure – should be an integral component of standard care for COPD. The optimal management of dyspnea in patients with advanced COPD is, however, an often neglected aspect in the continuum of care (5,6). In a recent Canadian multicentre study (7), relief of symptoms such as dyspnea was a top priority targeted for improvement in the care provided to patients hospitalized with COPD.

Dyspnea is a complex symptom arising from the interaction and dependence of various signals and processes including an individual's reactions and perceptions. The present document is not intended to review or explore the mechanisms of dyspnea in this setting – readers are advised to consult appropriate reference material (8-10).

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TABLE 1
Strength of evidence and grading of recommendations

Quality of evidence	
Grade A	Well-designed randomized controlled trials with consistent and directly applicable results
Grade B	Randomized trials with limitations including inconsistent results or major methodological weaknesses
Grade C	Observational studies, and from generalization from randomized trials in one group of patients to a different group of patients
Strength of recommendations	
Grade 1	Strong recommendation, with desirable effects clearly outweighing undesirable effects (or vice versa)
Grade 2	Weak recommendation, with desirable effects closely balanced with undesirable effects

Adapted from references 13 and 15

The present guideline statement presupposes that appropriate pharmacological therapies including short- and long-acting bronchodilator therapies, inhaled corticosteroids in combination with long-acting beta-2 agonists, theophylline preparations and nonpharmacological therapies including pulmonary rehabilitation, have been and continue to be optimally used in the management of dyspnea for patients with advanced COPD.

There remain many questions, clinical care gaps and treatment barriers regarding the optimal management of dyspnea in patients with advanced COPD and, specifically, whether various therapeutic options are effective in this setting. The current document is intended to specifically address these important clinical issues, using an evidence-based systematic review process led by a representative interprofessional panel of experts in the field.

Target population

The present clinical practice guideline provides direction on managing dyspnea in patients with advanced COPD. For the purposes of the present guideline, patients with advanced COPD are defined as those with COPD associated with either a forced expiratory volume in 1 s of lower than 50% predicted, or a medical research council dyspnea score of 4 to 5 in the setting of progressive disease associated with a limited prognosis. The specific management goal is to reduce persistent dyspnea that is distressing at rest or with minimal activity despite optimal therapy of advanced lung disease (11).

Target users

The current document is intended for all health care professionals involved in the care of patients experiencing dyspnea associated with advanced COPD including respirologists, family physicians, internists, nurses and health care administrators.

Methodology

Guideline development process: The Canadian Thoracic Society (CTS) clinical practice guideline document on managing dyspnea in patients with advanced COPD was developed by an expert working group panel of representative professionals involved in the care of patients with advanced COPD. Membership included respirologists, family physicians, internists, nurses and health care administrators. The overall process was coordinated by the CTS Respiratory Guideline Committee and staff, with the assistance of a consultant librarian and methodology experts. The guideline was developed in accordance with the convention of the 23-item Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument (12) – the current gold standard in appraising the reporting of clinical practice guidelines. The research questions were prepared based on the working

group's recognition of clinical care gaps and the solicited needs of the target populations. Questions were constructed in accordance with a 'PICO' process, taking into consideration the Problem, Intervention, Comparison and Outcomes within each research question, thus ensuring that an appropriate and answerable question was constructed. This process also enabled the development of a literature search strategy that outlined the types of studies, main topics and terms, inclusion and exclusion criteria, as well as suitable databases in which to conduct the search. The strength of evidence was assessed and recommendations were graded as outlined in Table 1.

Literature search

Based on the criteria outlined in the search strategy for each of the research questions, MEDLINE, EMBASE, the Cochrane Library, the Canadian Medical Association InfoBase and the National Guideline Clearinghouse were searched for pertinent published literature between January 1996 and March 2009. In addition, supplementary references of selected papers and recent review articles were also scanned by the expert working group members for additional citations.

Evidence selection

An initial review of abstracts was performed to inform selection of articles for which the full text was required, with a minimum of two working group members assigned to each research question. Once full-text articles were retrieved, data extraction tables were used to systematically extract evidence from the included/relevant full-text articles based on the predetermined inclusion and exclusion criteria supporting the research question (Table 2). These tables were used to summarize and organize information (ie, study design, target population, interventions, outcomes, and functional and clinical significance of findings) for the formulation of recommendations and supporting narrative text. Complete data extraction tables are available as online supplemental material (www.respiratoryguidelines.ca/guideline/chronic-obstructive-pulmonary-disease or www.pulsus.com). Articles were evaluated for the following outcomes: reduction in dyspnea, improved exercise capacity, improved activity, improved QoL/health status, decreased exacerbations, decreased health care use and cost effectiveness. Narrative text of key evidence and conclusions supporting the recommendations were completed based on the data extracted.

Formulating recommendations

Decisions regarding the strength of recommendations were achieved through a formal consensus process whereby working group members assigned to each of the research questions considered the strength of the evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology (13). In addition, adverse effects, health benefits to patients, the burden on the patient associated with adherence to the recommendations, extent to which the evidence directly addresses the research question, and impact on morbidity, mortality and QoL were considered (13,14) by the expert working group members. Final consensus on the recommendations by the full committee was achieved via an open voting process. Extensive discussions were held to edit, correct and update the document.

External expert commentary and review

Expert reviewers identified by the working group and the Canadian Respiratory Guidelines Committee, on the basis of their clinical and methodological expertise, were invited to review the document. A draft of the clinical practice guidelines was circulated to the reviewers, feedback was gathered and relevant changes were incorporated into the document. Reviewers also used a short AGREE II (12) checklist to document their appraisal and enhance the usability of the document.

The present document, including the questions and content, will be regularly reviewed and updated to reflect the changing and growing body of evidence in this area. At minimum, after a two-year period, the literature will be reviewed for new evidence to further inform, revise or update the guideline recommendations.

TABLE 2
Literature search results informing recommendations

Section	Topic	Studies informing recommendations for practice, n (references)
I	Do anxiolytic and antidepressant medications reduce dyspnea and improve quality of life in stable patients with advanced COPD compared with usual care (control population)?	13 (18-30)
II	Do opioids reduce dyspnea and improve quality of life in stable patients with advanced COPD when used as an adjunct to optimal conventional treatment?	10 (34-43)
III	Do nonpharmacological interventions (use of a fan, chest vibration techniques, pursed-lip breathing, meditation, relaxation therapy or behavioral techniques) reduce dyspnea and improve quality of life in stable patients with advanced COPD compared with usual care (control population)?	38 (45-82)
IV	Does supplemental oxygen reduce dyspnea and improve quality of life in stable patients with advanced COPD compared with usual care (control population) in patients with hypoxemia, and in patients without hypoxemia?	12 (93-104)

COPD Chronic obstructive pulmonary disease

SECTION I

Question

Do anxiolytic and antidepressant medications reduce dyspnea and improve QoL in stable patients with advanced COPD compared with usual care (control population)?

Introduction

Anxiety, panic and depression are psychological disturbances common in patients with COPD. Depending on the screening methodology used and the population studied, prevalence ranges from 10% to 33% for generalized anxiety, 0% to 70% for panic attacks and 10% to 40% for depression (16,17). Dyspnea is a complex symptom that evokes strong emotional reactions of fear, distress, anxiety and panic (8). Conversely, affective state can modulate respiratory sensory thresholds and, therefore, exacerbate the perception of dyspnea (8). Measures of anxiety and depression correlate with impaired health-related QoL (HRQoL), physical and social functioning, and mortality in patients with COPD (16,17). It has been postulated that nonpharmacological and pharmacological strategies to treat anxiety and depression may be helpful in relieving dyspnea and improving HRQoL in patients with COPD. This section evaluates the evidence regarding medications with anxiolytic properties that reduce dyspnea and improve QoL in patients with advanced COPD.

Key evidence

A total of 106 abstracts were initially identified by the search process, of which 43 were selected for complete review. Thirteen studies fully met the criteria and were selected for data extraction and utilization.

Four studies (18-21) investigating the role of benzodiazepine-class (alprazolam in two, diazepam in two) anxiolytic medications in moderate to severe COPD were identified. Three studies were short-term (a few weeks), randomized, placebo-controlled, crossover trials in a small number of subjects (n=4 to n=29), while one article was a case report. There were conflicting results reported for relief of dyspnea. The largest study (20 [n=29]) compared alprazolam 0.5 mg twice daily with placebo. There was no change in chronic dyspnea (medical research council score), exercise-related dyspnea or distance travelled in a 12 min walk test (12MWT). Drowsiness was the most common side effect reported in the studies, although in general, benzodiazepines were well tolerated.

Buspirone is a serotonergic, anxiolytic medication used in the short-term treatment of generalized anxiety disorders. Two studies (22,23) that investigated the effect of buspirone on anxiety, dyspnea and exercise tolerance in patients with COPD were identified. Both studies were short term (a few weeks), randomized, placebo-controlled, crossover trials in a small number of subjects (n=11 and n=16) with stable COPD. There were conflicting results for the relief of dyspnea during exercise, improvement in exercise tolerance and anxiety between these two studies. Buspirone was generally well tolerated, with three subjects in one study (23) withdrawing due to dizziness and fatigue.

Three randomized placebo-controlled trials (RCTs) investigating the role of different tricyclic antidepressant medications in COPD were identified (24-26). Two studies that included patients with a history of depression (24,25) demonstrated no improvement in exercise tolerance as assessed by 12MWT. HRQoL improved in one (25) of two studies (25,26) as assessed by the sickness impact profile. In one small study of 12 subjects (24), improvement in 12MWT distance correlated with improvement in anxiety and depression scores. Antidepressant medication did not significantly improve dyspnea scores during daily activities (25,26) or a 12MWT (25). Anticholinergic side effects were common, occasionally leading to discontinuation of medication.

Another class of antidepressant medications with possible anxiolytic properties – the selective serotonin-reuptake inhibitors (SSRIs) – have also been used to treat patients with COPD and depressive symptoms. Four small studies were identified – two case series (27 [n=7], 28 [n=14]) and two RCTs (29 [n=23], 30 [n=28]). In one of the case series (27), all seven subjects reported a subjective improvement in dyspnea, whereas there was no difference in dyspnea domain score of the chronic respiratory questionnaire between SSRIs and placebo in an RCT (29). There was no significant change in 6 min walk test distance (30) or HRQoL (29,30). In general, there was low acceptance of treatment with SSRIs by the study subjects, primarily due to side effects.

Question #1

Do anxiolytic and antidepressant medications reduce dyspnea and improve QoL in stable patients with advanced COPD compared with usual care (control population)?

The following recommendation is based on evidence from 13 studies and expert consensus of the CTS COPD expert panel.

Recommendation #1

We recommend that anxiolytic and antidepressant medications not be routinely used for the management of dyspnea in patients with advanced COPD. (Grade of recommendation 2B)

Conclusions

The results of these studies demonstrate little or conflicting evidence supporting the use of benzodiazepines, buspirone, tricyclic antidepressants or SSRIs to relieve dyspnea in patients with advanced COPD. The impact of these medications on HRQoL was infrequently reported. The burden to patients related to side effects was significant, particularly for tricyclic and SSRI antidepressant medications. Larger RCTs assessing the effectiveness of anxiolytic medications using validated measurement tools for dyspnea and HRQoL in patients with COPD are required.

SECTION II

Question

Do opioids reduce dyspnea and improve QoL in stable patients with advanced COPD when used as an adjunct to optimal conventional treatment?

Introduction

Dyspnea is refractory to conventional treatment for up to 50% of patients with advanced COPD (31). Opioids have been advocated as a potential treatment for refractory dyspnea in this population (32-34). It has been postulated that opioids modulate dyspnea via the following mechanisms: reducing minute ventilation, increasing ventilatory efficiency during exercise, reducing ventilatory responses to hypoxemia and hypercapnia, and effecting bronchoconstriction (1). Therefore, the Committee sought to explore the evidence regarding the use of opioids to treat dyspnea in patients with advanced COPD.

Key evidence

The literature search identified 165 citations, of which 156 were excluded after review. Of the nine citations meeting the inclusion criteria, one was a systematic review (34), which included four of the remaining citations and referred to 14 additional studies not identified in the search. Of the remaining four citations, one study was a four-day crossover RCT (35), one was a meta-analysis of the effects of nebulized opioids (36), one concerned epidural use of methadone (37) and one was an abstract of a substudy that focused on opioid responsiveness, which was subsequently published as a full-length article (38). The systematic review published in 2002 by Jennings et al (34) concluded that oral opioids (in 116 subjects) were effective in the treatment of dyspnea (16% improvement in dyspnea intensity; $P < 0.001$), while nebulized opioids were not; the latter was confirmed in a meta-analysis published later (36). All studies included in the two reviews were small. Jennings et al (34) reviewed 18 RCTs, the largest of which included 19 patients; there were nine single-dose studies of a nebulized opioid, and of nine studies involving either oral ($n=8$) or subcutaneous opioids ($n=1$), five were single- and four were multidose studies, one of diamorphine (39) (not available in Canada), two of dihydrocodeine (40,41) and one of morphine (42). Primary outcome measures have focused on dyspnea scores, and only one study reported an HRQoL assessment (chronic respiratory questionnaire) with an overall neutral effect (42).

The Committee formally extended the search of the Cochrane, EMBASE and Medline databases to February 5, 2010, revealing a 2010 update of the Jennings et al systematic review that included only one new RCT (35) involving 48 patients in a four-day crossover trial of sustained-release morphine (20 mg) versus placebo. In this, the only adequately powered multidose RCT published to date, morphine conferred beneficial effects on both morning ($P=0.01$) and evening ($P < 0.05$) visual analogue scores of dyspnea, and beneficial effects on sleep ($P=0.04$).

Given the dearth of adequately powered, clinically relevant RCTs, we have included mention of a significant body of work published to date in abstract form only (43). This concerns an open-label dose-finding study of 48 patients with COPD taking 10 mg, 20 mg or 30 mg of sustained-release morphine daily. Follow-up was for a minimum of three months, and using an assessment of 'overall clinical benefit', 51% of patients experienced sufficient benefit from fixed-dose opioids that they desired to continue therapy.

Conclusions

The evidence suggests that opioids reduce dyspnea in stable patients with advanced COPD when used as an adjunct to optimal conventional treatment. The American College of Chest Physicians recently released a consensus statement regarding the management of dyspnea in patients with advanced lung and heart disease (11), and also concluded that opioids should be considered and titrated for relief of dyspnea in the individual patient.

Question #2

Do opioids reduce dyspnea and improve QoL in stable patients with advanced COPD when used as an adjunct to optimal conventional treatment?

The following recommendation is based on evidence from 10 studies and expert consensus of the CTS COPD expert panel.

Recommendation #2

We recommend that oral (but not nebulized) opioids be used for the treatment of refractory dyspnea in the individual patient with advanced COPD. (Grade of recommendation 2C)

SECTION III

Question

Do nonpharmacological interventions (use of a fan, chest vibration techniques, pursed-lip breathing, meditation, relaxation therapy or behavioural techniques) reduce dyspnea and improve QoL in stable patients with advanced COPD compared with usual care (control population)?

Introduction

Pharmacological interventions alone do not typically provide adequate relief of dyspnea for some individuals (44). Nonpharmacological therapies that modify the emotional and/or cognitive experience of dyspnea may be helpful in reducing breathlessness in the clinical setting. The Committee reviewed the evidence regarding the efficacy of non-pharmacological interventions to reduce dyspnea.

Key evidence

The literature search identified 310 citations, of which 294 were excluded after review. A total of 14 studies with 1070 participants satisfied the inclusion criteria, while the remaining two articles were systematic reviews. Two studies (45,46) examined the effects of chest wall vibration, while four studies investigated the effects of pursed-lip breathing on dyspnea (47-50). Three studies addressed aspects of self-efficacy: dyspnea self-management to improve self-efficacy for dyspnea and walking (51); cognitive behavioral therapy and COPD education (52); and a self-management program (53). One systematic review (54) noted that all chronic disease management projects involving primary care for individuals with COPD showed improved QoL; however, the quality of the RCTs was not optimal and more research is needed in this area, including in populations that are clinically meaningful. Two methods of relaxation were examined by Louie (55). Single studies investigating the following interventions were identified: singing (56); heart rate variability biofeedback (57); and specialized respiratory home nursing care (58).

The 2008 Cochrane systematic review on nonpharmacological interventions for breathlessness in advanced stages of malignant and nonmalignant disease (44) yielded evidence on nonpharmacological strategies specific to patients with COPD that had not been identified in the initial literature search. These included RCTs (1996 to 2008) of acupuncture/acupressure (59-61), distractive auditory stimuli (music) (62-66), walking aids (67-72), chest wall vibration (73), neuromuscular stimulation (74-76), use of a handheld fan (77), counselling and support (78), breathing retraining (79), case management (80,81) and psychotherapy (82). In total, they constituted 24 additional articles that met the criteria for the present review, with the extracted data used to inform the recommendations.

Conclusions

Much of the evaluation of nonpharmacological interventions for the relief of dyspnea has involved subjects with COPD, although not necessarily in persons with advanced disease.

In accordance with the conclusions of Bausewein et al (44), we agree that the evidence supporting neuromuscular electrical muscle stimulation (NMES) is quite strong. NMES over four to six weeks

helps to relieve breathlessness in patients with COPD, which may be especially helpful for persons who are not capable of exercise. All studies showed that NMES improved dyspnea, muscle strength and performance in daily tasks.

Chest wall vibration is another nonpharmacological therapy that has strong supportive evidence for relief of breathlessness, although the chest wall vibration studies have only been tested in a laboratory setting. Although the exact process remains to be determined, the underlying mechanism of chest wall vibration is possibly related to the activation of muscle spindles in the intercostal muscles, with consequent modification of respiratory sensations.

Moderate evidence supports the use of walking aids, such as rollators, and breathing training. The positive effect of a walking aid on dyspnea is likely the result of the decreased work of breathing by bracing the arm(s) on the aid and assuming a forward-leaning posture. In addition, stabilization of the ribcage may improve accessory muscle function, thereby allowing these muscles to be engaged in respiratory efforts. Breathing training may take the form of pursed-lip or diaphragmatic breathing. Pursed-lip breathing may decrease respiratory rate and increase vital capacity, thereby improving gas exchange.

There is insufficient evidence and a lack of consensus to make an overall recommendation on the effectiveness of other general nonpharmacological interventions for reducing dyspnea and improving QoL in stable patients with COPD. At this time, there is insufficient evidence to recommend the routine use of acupuncture, acupressure, distractive auditory stimuli (music), relaxation, handheld fans, counselling and support programs, or psychotherapy.

Question #3

Do nonpharmacological interventions (use of a fan, chest vibration techniques, pursed-lip breathing, meditation, relaxation therapy or behavioural techniques) reduce dyspnea and improve QoL in stable patients with advanced COPD compared with usual care (control population)?

The following recommendations are based on evidence from 38 studies and expert consensus of the CTS COPD expert panel.

Recommendation #3a

NMES and chest wall vibration are helpful in reducing dyspnea in patients with COPD. We recommend that NMES and chest wall vibration, undertaken by knowledgeable providers, be used in the management of dyspnea in patients with advanced COPD. (Grade of recommendation 2B)

Recommendation #3b

COPD patients with dyspnea benefit from the use of walking aids. It is recommended that patients with advanced COPD be informed of the potential benefits of walking aids and undergo professional assessment for choosing a suitable device. (Grade of recommendation 2B)

Recommendation #3c

Pursed-lip breathing can be an effective strategy for relief of dyspnea. It is recommended that patients with advanced COPD be informed of the potential benefits of pursed-lip breathing and be instructed in its use. (Grade of recommendation 2B)

There is insufficient evidence to recommend the routine use of acupuncture, acupressure, distractive auditory stimuli (music), relaxation, handheld fans, counselling and support programs, or psychotherapy.

SECTION IV

Question

Does supplemental oxygen reduce dyspnea and improve QoL in stable patients with advanced COPD compared with usual care (control population) in patients with hypoxemia, and in patients without hypoxemia?

Introduction

Long-term oxygen therapy (LTOT) is regularly used in the management of patients with COPD complicated by severe hypoxemia. Two RCTs, published almost 30 years previously (83,84), established the significant survival benefit of LTOT when used for at least 15 h/day in hypoxemic COPD patients. On the other hand, a more recent study in COPD patients with moderate hypoxemia (PaO_2 of 56 mmHg to 65 mmHg) (85) did not demonstrate a survival benefit from oxygen therapy, although many subjects used oxygen for less than 15 h/day.

Many studies have also demonstrated improvement in exercise capacity and dyspnea from the use of intermittent, short-term ambulatory oxygen in patients with COPD. These studies have been systematically reviewed elsewhere (86,87). Multifactorial mechanisms have been proposed to explain the improvements in exercise performance with hyperoxia, including reduced respiratory frequency and minute ventilation, reduced dynamic hyperinflation and decreased dyspnea (88,89). The short-term use of supplemental oxygen in patients with advanced COPD has also been examined. Some studies reported a reduction in dyspnea with supplemental oxygen administration (90,91), while others did not (87,88,92).

It is unclear whether improvements in survival using LTOT or in exercise performance during short-burst oxygen use during laboratory or field exercise tests also translate into improvements in dyspnea experienced by patients with advanced COPD. Therefore, the committee examined whether the use of supplemental oxygen reduced dyspnea in patients with advanced COPD with or without hypoxemia.

Key evidence

Sixty-nine abstracts were initially identified in the search process, of which 28 were selected for complete review. Twelve studies fully met the inclusion criteria and were selected for data extraction.

Six studies examined the role of LTOT in COPD patients with severe resting hypoxemia. The earliest published study reviewed was a randomized, double-blind, placebo-controlled crossover trial (93) (five weeks in each arm with a two-week washout) of oxygen versus air in nine subjects with COPD. There was no significant difference in activity levels with oxygen versus air. Three studies compared COPD subjects on oxygen therapy ($n=23$ to $n=55$) with COPD case controls ($n=18$ to $n=53$) for six months (94-96). A low baseline HRQoL in COPD subjects requiring LTOT compared with COPD control subjects matched for age, sex and degree of airflow obstruction was noted in two studies (95,96). One study (94) documented slight improvement in neuropsychiatric functioning, but not in HRQoL with LTOT, while another reported no improvement in HRQoL with LTOT. In contrast, a significant improvement in HRQoL, but not in exercise capacity, anxiety or depression scores, was recently found (96). Finally, two prospective studies followed 26 and 114 COPD patients on LTOT for six months (97) and 12 months (98), respectively. Both studies reported limited effects of LTOT on HRQoL, depression or other psychological measures.

Six studies examined the role of ambulatory oxygen in COPD: four studies in subjects not on LTOT (ie, without severe resting hypoxemia) (99-102), one study in subjects on continuous LTOT for severe resting hypoxemia (103) and one study that included both groups of COPD subjects (104). All studies were randomized and double-blinded (oxygen versus air cylinders), and ranged from eight to 36 weeks in duration using different study designs. In COPD subjects without severe resting hypoxemia, ambulatory oxygen was reported to have no benefit compared with air in terms of changes in HRQoL or dyspnea in three of the four studies. In addition, acute effects of oxygen administered during a field or laboratory exercise test could not predict who would respond to ambulatory oxygen at home. The addition of ambulatory oxygen to COPD subjects already on continuous LTOT for severe resting hypoxemia resulted in no improvement in dyspnea, HRQoL or exercise capacity (103). Similarly, Sandland et al (104) reported no significant improvements in dyspnea, HRQoL or activity level. Most recently, a double-blinded RCT of air versus oxygen (105)

TABLE 3
Summary of evidence-based recommendations and grading

Recommendation	Description	Grade
1	We recommend that anxiolytic and antidepressant medications not be routinely used for the management of dyspnea in patients with advanced COPD	2B
2	We recommend that oral (but not nebulized) opioids be used for the treatment of dyspnea in the individual patient with advanced COPD	2C
3a	Neuromuscular electrical stimulation and chest wall vibration are helpful in reducing dyspnea in COPD. We recommend that neuromuscular electrical stimulation and chest wall vibration, undertaken by knowledgeable providers, be utilized in the management of dyspnea in advanced COPD patients	2B
3b	COPD patients with dyspnea benefit from the use of walking aids. It is recommended that patients with advanced COPD be informed of the potential benefits of walking aids, and undergo professional assessment for a suitable walking aid	2B
3c	Pursed-lip breathing can be an effective strategy for relief of dyspnea. It is recommended that patients with advanced COPD be informed of the potential benefits of pursed-lip breathing and be instructed in its use	2B
4	Continuous oxygen therapy for hypoxemic COPD patients reduces mortality, and may reduce dyspnea in some patients. The CTS has previously recommended that patients with advanced COPD who are hypoxemic at rest receive long-term continuous oxygen therapy because of a mortality benefit. Oxygen therapy may also provide symptomatic benefit by reducing dyspnea when administered at rest to hypoxemic patients with advanced COPD	2B

COPD Chronic obstructive pulmonary disease; CTS Canadian Thoracic Society

demonstrated similar reductions in dyspnea in stable nonhypoxemic patients with refractory dyspnea (64% of the study population had COPD).

Conclusions

While oxygen therapy is the standard of care for the treatment of hypoxemic patients with advanced COPD, only a few studies have objectively assessed the short-term effects of supplemental oxygen therapy on dyspnea at rest in patients with advanced COPD, and the results were mixed. Short-term supplemental oxygen with activity may improve exercise performance, enhance exercise training and reduce dyspnea in patients with COPD.

There is no evidence to support or not support the use of supplemental oxygen at rest or with activity in nonhypoxemic patients with advanced COPD.

Question #4

Does supplemental oxygen reduce dyspnea and improve QoL in stable patients with advanced COPD compared with usual care in patients with hypoxemia, and in patients without hypoxemia?

The following recommendation is based on evidence from 10 studies and expert consensus of the CTS COPD expert panel.

Recommendation #4

Continuous oxygen therapy for hypoxemic COPD patients reduces mortality, and may reduce dyspnea in some patients. The CTS has previously recommended that patients with advanced COPD who are hypoxemic at rest receive long-term continuous oxygen therapy because of a mortality benefit. Oxygen therapy may also provide symptomatic benefit by reducing dyspnea when administered at rest to hypoxemic patients with advanced COPD. (Grade of recommendation 2B)

There is no evidence to support the routine use of supplemental oxygen to reduce dyspnea in nonhypoxemic patients with advanced COPD. There appears to be little benefit from supplemental oxygen on QoL in patients with advanced COPD.

DISCUSSION

The present guidelines process was initiated with the belief, shared by others (11), that many patients with advanced COPD are not currently being treated consistently and effectively for relief of dyspnea. The purpose was to provide guidance to improve the treatment of dyspnea in this patient population. The present clinical practice guideline has addressed several clinically meaningful questions regarding the management of dyspnea in patients with advanced COPD, using an evidence-based, systematic review process led by a representative interprofessional

panel of experts in the field. The evidence from the literature reviews, and the experience and guidance afforded by the expert working group members enabled the formulation of relevant recommendations, fully recognizing that there are significant and large gaps in the scientific literature in this area (Table 3).

The evidence supports the benefits of oral (but not nebulized) opioids, NMES, chest wall vibration, walking aids and pursed-lip breathing in the management of dyspnea in the individual patient with advanced COPD. Supplemental oxygen is recommended for COPD patients with significant resting hypoxemia, but its use for the targeted management of dyspnea in this setting should be reserved only for patients who receive symptomatic benefit.

There is insufficient evidence in the literature to support the routine use of anxiolytic medications, nebulized opioids, acupuncture, acupressure, distractive auditory stimuli (music), relaxation, handheld fans, counselling and support programs, or psychotherapy. There is also no evidence to support the routine use of supplemental oxygen to reduce dyspnea in nonhypoxemic patients with advanced COPD.

To better manage dyspnea in this setting, it is vital to appreciate and understand its presence and severity.

Furthermore, for these recommendations to be applied in the management of dyspnea in patients with COPD, clinicians and clinical documentation must regularly and serially assess the patient experience of dyspnea. Multiple tools exist for assessing dyspnea and, although no consensus exists for the correct clinical assessment strategy, other bodies have suggested that, at a minimum, some measure of the symptom intensity and some inquiry into the distress to the patient associated with the dyspnea be used to guide management (11,106-108). Patients with advanced COPD should be routinely asked to rate the intensity of their shortness of breath as a fundamental aspect of their care (11). In addition, appropriate pharmacological therapies – including short- and long-acting bronchodilator therapies, inhaled corticosteroids in combination with long-acting beta-2 agonists and theophylline preparations as well as nonpharmacological therapies including pulmonary rehabilitation should be appropriately used in the management of dyspnea for patients with advanced COPD (109,110).

Opioids are infrequently prescribed in this setting, despite the evidence supporting their benefit. Several issues contribute to this reality including unfamiliarity with dosing, concerns regarding respiratory depression and/or addiction, the fear of other significant side effects, as well as concerns and attitudes about addiction and dependence. An additional obstacle to the optimal management of dyspnea in advanced COPD has been a lack of attention in some clinical guideline statements. Standards from the European Respiratory Society and the American Thoracic Society make no recommendation (111) regarding opioid use. An earlier consensus document from the American

TABLE 4
Suggested protocol for managing dyspnea with opioid therapy in advanced chronic obstructive pulmonary disease patients

- Initiate opioid therapy with oral immediate-release morphine syrup – titrate slowly at weekly intervals over a 4- to 6-week period
- Start therapy with morphine 0.5 mg orally twice daily for 2 days, and then increase to 0.5 mg orally every 4 h while awake for remainder of week 1
- If tolerated and indicated, increase to morphine 1.0 mg orally every 4 h while awake in week 2, increasing by 1.0 mg/week or 25% dosage increments/week until the lowest effective dose that appropriately manages the dyspnea is achieved
- Once a stable dosage is achieved (ie, no significant dose change for 2 weeks and dyspnea managed), a sustained-release preparation at a comparable daily dose could be considered for substitution
- If patients experience significant opioid-related side effects such as nausea or confusion, substitution of an equipotent dose of oral hydromorphone could be considered (1 mg hydromorphone = 5 mg morphine)
- Stool softeners and laxatives should be routinely offered to prevent opioid-associated constipation

Adapted from references 1, 109 and 115

Thoracic Society (112) specifically recommended against the use of opioids in patients with COPD except in the terminal stages. The Global Initiative for Chronic Obstructive Lung Disease stated that “... some clinical studies suggest morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive individuals” (113), although that concern has recently been challenged (1). Conversely, the Canadian (109) and Australian (114) COPD guidelines included recommendations for considering opioids in the management of severe dyspnea. The Canadian COPD guidelines published in 2007 (109) specifically stated that “opioids remain the most effective dyspnea-relieving medication in end-of-life care”, and included a table listing various opioid medications, mode of administration and commonly used dosages. The recent policy statement from the American College of Chest Physicians (6) and the American Thoracic Society statement (5) on palliative and end-of-life care also appropriately addressed the use of opioids in this setting.

Although providing a pathway for prescribing opioid therapy in patients with advanced COPD was not an intended goal, the Committee did recognize and appreciate the current unfamiliarity with prescribing and dosing. A potential approach to the initiation and continuation of opioid therapy targeted to managing dyspnea in patients with advanced COPD is provided in Table 4 (1), and has been discussed elsewhere (109,115). The role of opioid therapy and other therapies in the comprehensive management of refractory dyspnea in patients with advanced COPD is outlined in Figure 1.

FUTURE RESEARCH NEEDS

It has become apparent from this process that there is a paucity of high-quality evidence, scientific literature and information regarding this topic. Further study is required to address many important clinical questions, and to provide further understanding of dyspnea in this setting. Larger RCTs assessing the effectiveness of anxiolytic medications using validated measurement tools for dyspnea and HRQoL in COPD are required. The contributions and effects of managing depression and anxiety on dyspnea also require further study. Research of the use of supplemental oxygen in this setting is necessary. Regarding opioids, several important clinical questions remain unanswered (1). Although opioids have proven to be beneficial, the optimal initiation dose, dosing interval, titration schedule and delivery route are not well understood. To what degree are beneficial effects or adverse effects of opioids sustained over time? Can the available data supporting oral opioids for dyspnea translate to intravenous therapy as it does in general palliative care management for those patients unable to use the oral route? Does adherence to opioid therapy change over time, and what are the

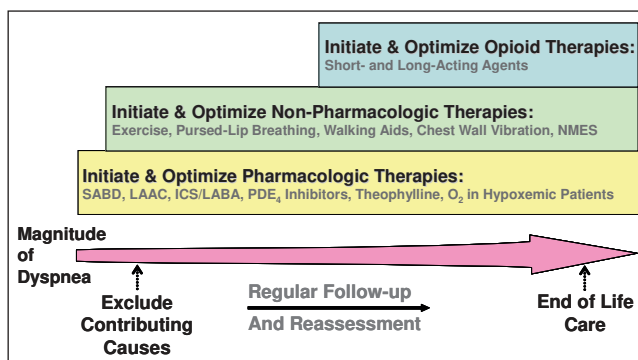


Figure 1) Comprehensive approach to management of dyspnea in patients with advanced chronic obstructive pulmonary disease (COPD). ICS Inhaled corticosteroids; LAAC Long-acting anticholinergics; LABA Long-acting beta-2 agonists; NMES Neuromuscular electrical stimulation; O₂ Oxygen; PDE₄ Phosphodiesterase 4; SABD Short-acting bronchodilators. Adapted from references 109, 110 and 115

factors (ie, side effects, patient/caregiver fears or misconceptions about addiction and dependence, or fears about opioids hastening death) that influence adherence? Are some opioids more efficacious or tolerated better than others? Are patients with advanced COPD at a higher risk of opioid-induced complications than other patients with severe dyspnea, and are conventional concerns with appropriately dosed and monitored opioids in patients with hypercapnia justified? Other important areas also require further study including whether the benefits from NMES realized in the research laboratory are fully transferable to the clinical setting. These important research questions require attention to advance our understanding in this area.

KNOWLEDGE TRANSFER AND TOOLS FOR PRACTICE

In addition to publication, the present document will be posted at www.respiratoryguidelines.ca and www.pulsus.com for viewing and download. A teaching and dissemination slide kit, complementing existing CTS teaching aids for the diagnosis and management of COPD, is being developed and will be similarly posted for viewing and download. Patient/family/caregiver and health care professional information sheets (two in total) will be posted for viewing and download, and also further disseminated by the Canadian and provincial lung associations. Finally, a trifold pocket ‘Slim Jim’ summarizing key recommendations and information from this clinical practice guideline will be forwarded to all family physicians in Canada, provincial Ministries of Health, and selected provincial and regional health authorities.

The Working Group recognized and acknowledged potential barriers to the more widespread use of opioids in this setting, the lack of specific protocols and familiarity with the use of NMES, and the potential limitation of sufficiently trained individuals to deliver these effective techniques. The Committee is hopeful that the present document and the above tools and strategies will assist in the meaningful dissemination and implementation of the recommendations from the present guideline statement into clinical practice.

It is also recommended that the development of reliable and responsive quality measures in dyspnea management – grounded in the recommendations presented in the current document – will facilitate the evaluation, implementation and health care delivery improvement in this setting (106).

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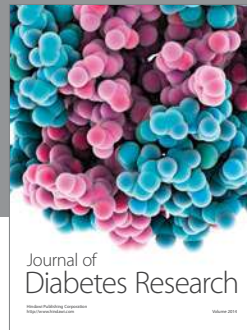
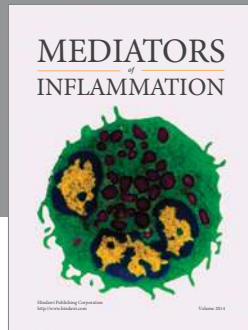
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