Prevalence and Pharmacologic Treatment of Breathlessness in Severe Chronic Obstructive Pulmonary Disease

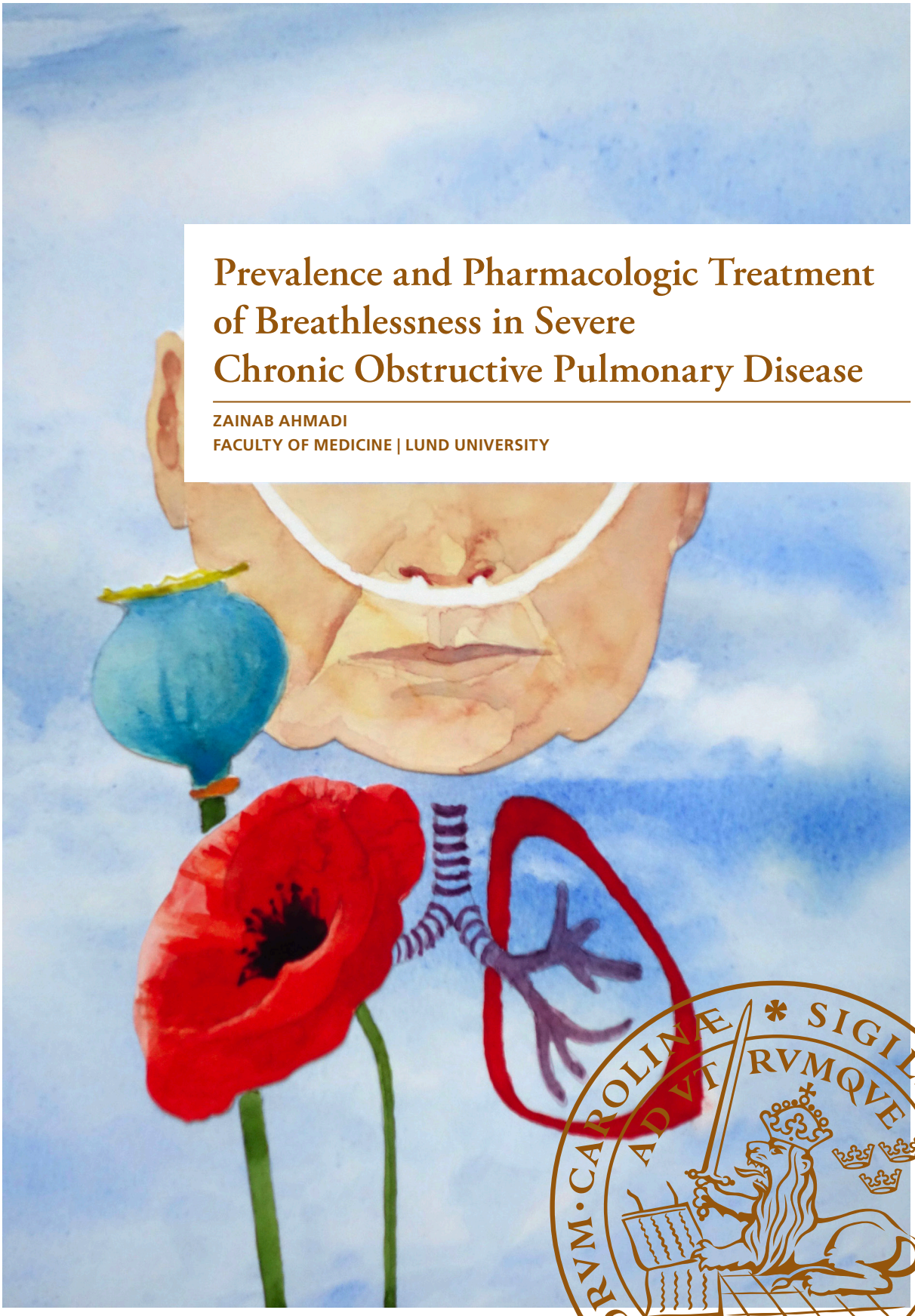
Ahmadi, Zainab

2019

Document Version:
Publisher's PDF, also known as Version of record

Prevalence and Pharmacologic Treatment of Breathlessness in Severe Chronic Obstructive Pulmonary Disease

ZAINAB AHMADI
FACULTY OF MEDICINE | LUND UNIVERSITY



Prevalence and Pharmacologic Treatment of Breathlessness in Severe Chronic Obstructive Pulmonary Disease

Prevalence and Pharmacologic Treatment of Breathlessness in Severe Chronic Obstructive Pulmonary Disease

Zainab Ahmadi
MD

LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Lecture Room 3, Entrégatan 7, Skåne University Hospital, Lund
June 7, 2019, 09:00.

Faculty opponent
Assistant Professor Daisy J.A. Janssen

Maastricht University Medical Center+, Netherlands

Organization	Document name
LUND UNIVERSITY **Department of Clincal Sciences Lund, Respiratory Medicine & Allergology**	**DOCTORAL DISSERTATION**
	Date of issue **7 JUNE 2019**
Author **ZAINAB AHMADI, MD**	Sponsoring organization None

Title and subtitle

PREVALENCE AND PHARMACOLOGIC TREATMENT OF BREATHLESSNESS IN SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Chronic breathlessness is a feared and distressing symptom with significant impact on daily life. Little is known of the prevalence of breathlessness at the end of life in severe COPD. International guidelines support the use of opioids to treat breathlessness, but it is unknown how commonly opioids are prescribed for the indication of breathlessness. Supplemental oxygen therapy is commonly prescribed, but data is conflicting on its efficacy in treating breathlessness. Knowledge of physician ability to identify chronic breathlessness and readiness to treat breathlessness with opioids is limited.

Aims:

- To evaluate the prevalence of symptoms and their management at the end of life in patients with oxygen-dependent COPD in Sweden,compared to those with cancer (Study I).
- To quantify the reported indications for opioid prescriptions in oxygen-dependent COPD in Sweden (Study II).
- To investigate the efficacy of supplemental oxygen therapy for breathlessness in COPD patients with no or mild hypoxemia (Study III).
- To assess recognition and treatment of chronic breathlessness as compared to chronic pain by physicians in Sweden, using a case-based survey (Study IV).

Methods: Nationwide register-based cohort study of patients with oxygen-dependent COPD from the Swedevox register linked with the Swedish Register of Palliative Care (Study I) and with the Swedish Prescribed Drug Register (Study II). Cochrane systematic review and meta-analysis of the efficacy of supplemental oxygen therapy for breathlessness (Study III). Randomised, controlled, double-blind, parallel-group, web-based trial of Swedish physicians treating a hypothetical patient with COPD and severe breathlessness versus a patient with severe pain (Study IV).

Results and conclusions: At the end of life, breathlessness was three times more common in patients with COPD than in those with cancer (Study I). Opioids were commonly prescribed for pain in oxygen-dependent COPD patients but rarely to treat breathlessness, which represented 2% of the stated indications (Study II). Supplemental oxygen therapy modestly reduced breathlessness during exercise, but there was no evidence of an effect on performance of daily activities or on quality of life (Study III). In a case presentation of a COPD patient, severe chronic breathlessness was less likely to be identified by physicians as requiring symptomatic treatment and also less likely to be treated with opioids as compared to a patient severe pain (Study IV).

Key words

Chronic obstructive pulmonary disease, Breathlessness, Treatment, End of life care, Symptoms, Oxygen, Opioids

Supplementary bibliographical information	Language
Lund University, Faculty of Medicine Doctoral Dissertation Series 2019:58	**ENGLISH**
ISSN and key title **1652-8220 PREVALENCE AND PHARMACOLOGIC TREATMENT OF BREATHLESSNESS IN SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE**	ISBN **978-91-7619-787-5**

Recipient's notes	Number of pages 90	Price
	Security classification	

Signature  Date 2019-05-02

Prevalence and Pharmacologic Treatment of Breathlessness in Severe Chronic Obstructive Pulmonary Disease

Zainab Ahmadi
MD

LUND
UNIVERSITY

Cover photo by Derek Mundell

Lund University, Faculty of Medicine Doctoral Dissertation Series 2019:58
Department of Clinical Sciences, Respiratory Medicine and Allergology, Lund

ISBN 978-91-7619-787-5
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2019

To my family for their love and support

Table of Contents

Thesis at a glance

Study	Aims	Methods	Results	Significance
I	To evaluate the prevalence of symptoms and their management at the end of life in patients with oxygen-dependent COPD in Sweden, compared to those with cancer.	Nationwide register-based cohort study of prevalence of symptoms and end of life care in patients with oxygen-dependent COPD who died between 2011-2013. Patients in Swedish Register of Palliative Care who died from cancer during the same time period were included as the comparator group.	Breathlessness was three times more common in patients with COPD than in those with cancer in the last week of life. COPD patients were found to have limited access to specialized care services and to receive less end of life care than patients with cancer in Sweden.	Paper I highlights the need of adequate end of life care among patients with advanced COPD, including optimal symptom management especially of breathlessness and increased access to specialized palliative care services.
II	To quantify the reported indications for opioid prescriptions in oxygen-dependent COPD in Sweden.	Longitudinal, population-based cohort study. Data fom all patients starting oxygen therapy for COPD in the Swedewox register between 2005-2009 were linked with the Swedish Prescribed Drug Register. A random sample (n=2,000) of their dispensed opioid prescriptions was obtained and the indications were analyzed.	Opioids were commonly prescribed for pain in oxygen-dependent COPD patients, but rarely to treat breathlessness, which accounted for only 2% of the stated indications.	Paper II highlights the need of practical guidelines on how to implement available evidence-based treatment of breathlessness in clinical practice.
III	To investigate the efficacy of supplemental oxygen therapy for breathlessness in COPD patients with no or mild hypoxemia.	Cochrane systematic review and meta-analysis of the efficacy of supplemental oxygen therapy for breathlessness. All randomized controlled trials published through July 2016 were reviewed and meta-analyses were perfomed.	Supplemental oxygen therapy modestly reduced breathlessness during exercise in COPD with no or mild hypoxemia, but there was no evidence of an effect in daily life or on quality of life.	Paper III confirms that oxygen therapy can decrease breathlessness during exercise in the laboratory setting, such as in a pulmonary rehabilitation program. However it should not be routinely offered at home to patients for relief of breathlessness because of a lack of effect in daily life and on quality of life.
IV	To assess recognition and treatment of chronic breathlessness as compared to chronic pain by physicians in Sweden, using a case-based survey.	Randomized, controlled, double-blind, parallel-group, web-based trial. Swedish physicians completed a survey of a hypothetical COPD patient with severe breathlessness versus severe pain. Primary outcomes were percentages of physicians who identified the need for symptomatic treatment and percentage offering opioid therapy. Secondary outcome was reasons for not treating with opioids.	In a case presentation of a COPD patient, severe chronic breathlessness was less likely to be identified by physicians as requiring symptomatic treatment and also less likely to be treated with opioids as compared to a patient with chronic pain.	Paper IV highlights the need to identify symptoms and their impact more actively, especially chronic breathlessness in COPD; and to actively consider evidence-based symptomatic treatment.

List of publications

The thesis is based on the following publications, referred to in the text by the Roman numerals I-IV.

I. Ahmadi Z, Lundström S, Janson C, Strang P, Emtner M, Currow DC, Ekström M.

End-of-life care in oxygen-dependent COPD and cancer: a national population-based study. Eur Respir J. 2015 Oct;46(4):1190-3.

II. Ahmadi Z, Bernelid E, Currow DC, Ekström M.

Prescription of opioids for breathlessness in end-stage chronic obstructive pulmonary disease: a national population-based study. International Journal of Chronic Obstructive Pulmonary Disease. 2016 Oct 21;11:2651-2657.

III. Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D.

Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. Cochrane Database Syst Rev. 2016 Nov 25;11: CD006429.

IV. Ahmadi Z, Sandberg J, Shannon-Honson A, Vandersman Z, Currow DC, Ekström M.

Is Chronic Breathlessness Less Recognized and Treated Compared with Chronic Pain?: A Case-Based Randomised Controlled Trial. Eur Respir J. 2018 Sep 15;52(3).

Accompanied by an editorial by Johnson MJ, Fallon M. **Chronic breathlessness: time for Cinderella to go to the ball!** Eur Respir J. 2018 Sep 15;52(3).

Publications not included in the thesis:

V. Ahmadi Z, Bornefalk-Hermansson A, Franklin K, Midgren B, Ekström M.

Hypo- and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. Respir Res. 2014 Mar 13;15:30.

VI. Ahmadi Z, Wysham N, Lundström S, Janson C, Currow DC, Ekström M.

End of life care in oxygen-dependent ILD compared to lung cancer: a national population-based study. Thorax. 2016 Jun;71(6):510-6.

VII. Ekström M, Vergo MT, Ahmadi Z, Currow DC.

Prevalence of sudden death in palliative care: data from the Australian Palliative Care Outcomes Collaborative. J Pain Symptom Manage. 2016 Aug;52(2):221-7.

VIII. Ahmadi Z, Sundh J, Bornefalk-Hermansson A, Ekström M.

Long-term oxygen therapy 24 vs 15 h/day and mortality in chronic obstructive pulmonary disease. PLoS One. 2016 Sep 20;11(9):e0163293.

IX. Ekström M, Ahmadi Z, Larsson H, Nilsson T, Wahlberg J, Ström KE, Midgren B.

A Nationwide Structure for Valid Long-Term Oxygen Therapy: 29 year prospective data in Sweden. Int J Chron Obstruct Pulmon Dis. 2017 Oct 30;12:3159-3169.

X. Sundh J, Ahmadi Z, Ekström M.

Daily duration of long-term oxygen therapy and risk of hospitalization in oxygen-dependent COPD patients. Int J Chron Obstruct Pulmon Dis. 2018 Aug 28;13:2623-2628.

Abstract

Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Chronic breathlessness is a feared and distressing symptom with significant impact on daily life. Little is known of the prevalence of breathlessness at the end of life in severe COPD. International guidelines support the use of opioids to treat breathlessness, but it is unknown how commonly opioids are prescribed for the indication of breathlessness. Supplemental oxygen therapy is commonly prescribed, but data is conflicting on its efficacy in treating breathlessness. Knowledge of physician ability to identify chronic breathlessness and readiness to treat breathlessness with opioids is limited.

Aims

- To evaluate the prevalence of symptoms and their management at the end of life in patients with oxygen-dependent COPD in Sweden, compared to those with cancer (Study I).
- To quantify the reported indications for opioid prescriptions in oxygen-dependent COPD in Sweden (Study II).
- To investigate the efficacy of supplemental oxygen therapy for breathlessness in COPD patients with no or mild hypoxemia (Study III).
- To assess potential recognition and treatment of chronic breathlessness as compared to chronic pain by physicians in Sweden, using a case-based survey (Study IV).

Study Design

Nationwide register-based cohort study of patients with oxygen-dependent COPD recorded in the Swedevox register linked with the Swedish Register of Palliative Care (Study I) and with the Swedish Prescribed Drug Register (Study II). Cochrane systematic review and meta-analysis of the efficacy of supplemental oxygen therapy for breathlessness (Study III). Randomized, controlled, double-blind, parallel-group, web-based trial of Swedish physicians treating a hypothetical patient with COPD and severe breathlessness versus a patient with severe pain (Study IV).

Results and conclusions

At the end of life, breathlessness was three times more common in patients with COPD than in those with cancer (Study I). Opioids were commonly prescribed for pain in oxygen-dependent COPD patients but rarely to treat breathlessness, which represented 2% of the stated indications (Study II). Supplemental oxygen therapy

modestly reduced breathlessness during exercise in COPD with no or mild hypoxemia, but there was no evidence of an effect in daily life or on quality of life (Study III). In a case presentation of a COPD patient, severe chronic breathlessness was less likely to be identified by physicians as requiring symptomatic treatment and also less likely to be treated with opioids as compared to a patient with chronic pain (Study IV).

Sammanfattning på svenska

Bakgrund

Kroniskt obstruktiv lungsjukdom (KOL) är associerad med hög sjuklighet och dödlighet över hela världen. Kronisk andfåddhet är ett ångestladdat och begränsande symptom med stor påverkan på patienters dagliga liv. Kunskapen är bristfällig kring förekomsten av andfåddhet i livets slutskede vid svår KOL. Internationella riktlinjer stödjer behandling med opioider (morfinpreparat) för att lindra andfåddhet men det är oklart hur vanlig indikationen andfåddhet är i opioidrecept. Syrgas förskrivs ofta för att lindra andfåddhet men det finns motstridiga data på effekten av syrgasbehandling vid andra indikationer än vid svår syrebrist. Det finns ingen tidigare studie om läkares förmåga att identifiera och behandla kronisk andfåddhet jämfört med smärta.

Syfte

- Studera förekomsten av symptom och symptomatisk behandling i livets slutskede vid svår KOL, jämfört med cancer (Studie I).
- Studera indikationer vid förskrivning av recept på opioider till patienter med svår KOL (Studie II).
- Studera effekten av syrgas för att lindra andfåddhet hos patienter med KOL som inte uppfyller kriterier för kontinuerlig hemsyrgas (Studie III).
- Studera om det föreligger under-diagnostik och under-behandling av kronisk andfåddhet jämfört med kronisk smärta utifrån en fallbeskrivning med en KOL patient (Studie IV).

Studiedesign

Nationell registerbaserad kohortstudie av patienter med KOL och hemsyrgasbehandling utifrån Swedevox registret som samkördes med Svenska Palliativregistret (Studie I) och med Svenska Läkemedelsregistret (Studie II). Cochrane systematisk översikt och meta-analys av effekten av behandling med syrgas på andfåddhet och livskvalité (Studie III). Randomiserad, kontrollerad, dubbelblindad, parallel-grupp, web-baserad studie bland läkare utifrån en hypotetisk fallbeskrivning där patienten lider av KOL och svår andfåddhet eller smärta (Studie IV).

Fynd och sammanfattning

I livets slutskede, var andfåddhet tre gånger vanligare hos KOL-patienterna än hos cancer patienter (Studie I). Opioider förskrevs mot smärta till KOL patienter men

sällan (2% av recepten med angiven indikation) för att behandla andfåddhet (Studie II). Syrgasbehandling kan ge en måttlig minskning av andfåddhet vid träning men det finns ingen evidens för att det är av nytta i dagligt liv eller för att förbättra livskvalitén hos patienter med svår KOL (Studie III). I en fallpresentation av en patient med KOL, kronisk andfåddhet var mindre sannolikt att identifieras av läkare som behandlingskrävande och att föranleda behandling med opioider (Studie IV).

Abbreviations

ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body mass index
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
EOL	End of life
EMGdi	Electromyogram of the diaphragm
EMGdi%max	Diaphragm electromyogram activity as a percentage of maximum
FEV_1	Forced expiratory volume in one second
FEV_1 % pred	FEV_1 as a percentage of predicted value
FiO_2	Fraction of inspired oxygen
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQOL	Health-related quality of life
ICD	International Classification of Disease
IQR	Interquartile range
I^2	I square, a measure of heterogeneity
LLN	Lower limit of normal
LTOT	Long-term oxygen therapy
MDP	Multidimensional Dyspnoea Profile
mMRC	modified Medical Research Council
OR	Odds Ratio
$PaCO_2$	Arterial blood gas tension of carbon dioxide
PaO_2	Arterial blood gas tension of oxygen
SD	Standard deviation
SMD	Standardized mean difference
SRPC	Swedish Register of Palliative Care
WHO	World Health Organization

Introduction

Chronic Obstructive Pulmonary Disease

Definition

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)

> "Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that are due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[1]

The most common respiratory symptoms in COPD include breathlessness, chronic cough, and/or sputum production [2]. Chronic airflow limitation is defined by GOLD as a post-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) below 0.70 [1, 3]. Chronic respiratory symptoms may precede the development of airflow limitation [4].

Epidemiology and outcomes

Chronic obstructive pulmonary disease is responsible for substantial morbidity and health-care expense worldwide [5]. Reported COPD prevalence, morbidity, and mortality vary across countries depending on factors including the diagnostic criteria, survey methods, and analytical methods. The global prevalence of COPD is approximately 11.7% (95% CI 8.4% – 15.0%) with three million deaths annually attributed to COPD as the main cause of death [1, 6]. The prevalence of COPD in the adult population of Sweden is approximately 10% [7, 8]. The burden of COPD is projected to increase over coming decades with the aging of world population and continued exposure to risk factors such as smoking and environmental pollution [9]. Exacerbations and comorbidities associated with severe COPD contribute to a significant economic burden on the healthcare system, mainly through hospitalization [10, 11].

Cigarette smoking is the most important single risk factor for developing COPD [12, 13]. In the 1970s, Fletcher *et al.* showed that, when compared to non-smokers,

most smokers showed an accelerated decline in lung function (susceptible smokers), although evidence of this more rapid decline was not found in some (non-susceptible) smokers [14]. Although smoking cessation is beneficial at all ages, quitting before age 45 appears to have a stronger beneficial effect on lung function [15, 16]. In recent years, it has been proposed that only half of COPD cases result from rapid decline in normal lung function related to adult smoking, with the remainder associated with low peak lung function in early adulthood followed by age-appropriate rates of decline [17]. Factors affecting early lung development include maternal smoking, low birth-weight, and severe childhood respiratory infections [18]. Strong evidence implicates occupational exposure and rare genetic syndromes such as alfa-1antitrypsin deficiency as causes of COPD [13, 19-22]. Additional factors associated with an increased risk of COPD include increased age [18], female sex [23], long-standing asthma [24], and outdoor pollution and biomass smoke [13, 25, 26]. The precise biological mechanisms underlying these observed associations remain largely unknown. Taken together, these factors lead to, in susceptible individuals, impaired lung growth and chronic inflammation with accelerated lung function decline and the development of COPD.

Pathophysiology

COPD is a heterogeneous, often progressive, inflammatory disease with pathological changes observed in the airways, alveoli, and pulmonary vasculature [27]. The small airways offer little resistance in the normal lung, but become the major site of airway obstruction in COPD [28, 29]. The disease process includes inflammatory and structural changes in the lungs, including chronic airway inflammation, loss of small airways, and destruction of the lung parenchyma. Together, these changes result in expiratory airflow limitation with inadequate lung emptying on expiration resulting in subsequent static and dynamic hyperinflation and impaired gas exchange [30].

Knowledge of the key molecular mechanisms responsible for the pathological changes seen in COPD is incomplete. It is proposed that an amplified inflammatory response to prolonged exposure to irritants such as cigarette smoke and other noxious particles, leading to persistent infiltration of the mucosa, submucosa, and glandular tissue by inflammatory cells, causes mucus plugging, epithelial cell hyperplasia, and wall thickening in airways of less than 2 mm diameter [31, 32]. These changes, together with dysregulated tissue repair due to an imbalance in protease-antiprotease activity, result in airway remodeling, loss of the small airways, and subsequent emphysematous destruction of the parenchyma [33-36]. In addition, peribronchiolar and interstitial fibrosis secondary to increased production of growth factors is reported in COPD [37]. Vascular injury by toxic agents and hemodynamic changes induced by hypoxia lead to the pulmonary vascular

remodeling seen in COPD and development of comorbidities such as pulmonary hypertension and right heart failure [38, 39].

In the past decade, COPD has been increasingly recognized as a systemic disease. According to one hypothesis, inflammatory proteins spill over from the lungs into the circulatory system, causing systemic inflammation and disease manifestations [40, 41]. Systemic conditions include cardiovascular comorbidities, cachexia and muscle dysfunction, osteoporosis, anemia, depression, and anxiety [42]. However, it is difficult to determine with certainty whether systemic manifestations are caused by COPD or reflect coexistent disease related to common risk factors such as smoking, inactivity, and aging [42, 43].

Increased airway inflammation occurs during COPD exacerbations triggered by bacterial or viral respiratory infections and by environmental pollutants [44]. Exacerbations are characterized by increased lung hyperinflation with reduced airflow and ventilation-perfusion abnormalities leading to hypoxemia [45, 46]. Pneumonia, venous thromboembolism, and heart failure may mimic or complicate COPD exacerbation [1, 44].

Assessment and Management

The presence of COPD should be considered in patients with chronic respiratory symptoms and a history of exposure to possible risk factors [47]. Spirometry is the reference standard for assessing the severity of airflow limitation in diagnosing COPD. A post-bronchodilator fixed FEV_1/FVC ratio of <0.70 is required for establishing a COPD diagnosis according to the 2019 GOLD report [1]. This criterion, however, does not take into account age-related decline in FEV_1/FVC ratio and may result in overdiagnosis of disease in the elderly and underdiagnosis in younger adults when compared with a population-derived, age-adjusted lower limit of normal (LLN) [48, 49]. The LLN values are based on the normal distribution and classify the bottom 5% of a healthy population as abnormal [50]. The use of the fixed ratio is supported by the finding that persons >65 years of age with a FEV_1/FVC ratio <0.70 have a worse prognosis, with increased risk of COPD-related hospitalization and death, even when FEV_1 is above the LLN [51].

According to updated GOLD recommendations, COPD assessment for guidance of treatment planning must consider the severity of airflow limitation, the magnitude of patient symptoms, the history of severe exacerbations, risk of recurrent exacerbations, and the presence of comorbidities [1]. The GOLD classification of airflow limitation severity is based on FEV_1 as a percentage of that predicted (FEV_1 % pred). Stages are mild ($FEV_1 \geq 80\%$ pred), moderate ($FEV_1 \geq 50\% - <80\%$ pred), severe ($FEV_1 \geq 30 - <50\%$ pred), and very severe ($FEV_1 <30\%$ pred) [1]. Patients with history of a single severe COPD exacerbation requiring hospitalization present

a higher risk of future severe exacerbations [52]. Symptom assessment tools such as the modified Medical Research Council (mMRC) scale (0 to 4 activity-anchored scale of breathlessness) and the COPD Assessment Test (eight questions to assess the impact of COPD on health status) are recommended to stratify and monitor disease progression [53, 54].

COPD treatment should be guided by the severity of lung impairment, symptom burden, and rate of recurrent exacerbations [1, 55]. Smoking cessation support and vaccination for pneumonia and influenza should be offered to all patients [1]. When breathlessness limits activity or quality of life, COPD should be treated with maintenance bronchodilation with long-acting beta2-agonists and/or long-acting muscarinic receptor antagonists as monotherapy or in combination [1]. Patients with acute exacerbations might benefit from triple therapy with addition of inhaled corticosteroids, particularly in the presence of elevated blood eosinophil levels [56, 57]. Pulmonary rehabilitation programs that include strength and endurance training, self-management education, and psychosocial support are effective and improve exercise tolerance, symptoms, and quality of life but are often underutilized [58]. Supplemental oxygen improves survival of patients with chronic severe resting hypoxemia [tension of arterial oxygen (PaO_2) on air <7.4 kPa] or moderate hypoxemia (7.4–8.0 kPa) together with signs of right-sided heart failure or secondary polycythemia (erythrocyte volume fraction >0.54) [59-61].

Comorbidities should be assessed routinely, diagnosed, and treated appropriately [62]. Selected patients might benefit from referral to a specialty clinic for consideration of bilevel noninvasive positive-pressure ventilation for those with chronic hypercapnic respiratory failure, surgical or bronchoscopic lung volume reduction for patients with severe emphysema and lung hyperinflation, or lung transplantation for patients younger than 70 years [63-65].

Despite optimal medical therapy, many COPD patients suffer from distressing breathlessness, anxiety, depression, and fatigue with poor symptom control for long periods of time as the disease progresses [66]. Compared to patients with cancer, palliative care is not commonly provided to patients with COPD, which may lead to a substantial symptom burden at the end of life (EOL) [67, 68]. Access to specialized palliative care services with prevention and management of symptoms at the EOL in patients with severe COPD in Sweden has not been previously assessed.

The focus of the research reported in this thesis was patients with severe COPD, defined as the need for supplemental oxygen therapy or severe airflow limitation with FEV_1 <50%.

Breathlessness

Definition

Breathlessness (dyspnea, shortness of breath) is defined as ‘a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity and that vary in their unpleasantness and in their emotional and behavioral significance’ [69]. Chronic breathlessness is defined as breathlessness that is disabling and persists despite the optimal treatment of reversible causes [70].

Breathlessness is considered a multidimensional symptom including sensory and affective aspects as well as impact on function [71]. Sensory aspects include ratings of intensity (quantity) and sensory descriptors (quality), often measured using unidimensional instruments such as visual analog scales, numerical rating scales, or the modified Borg scale [72-74]. Affective aspects involve perception of immediate unpleasantness, generally measured by unidimensional tools or multidimensional instruments assessing emotional responses such as anxiety. In recent years, instruments including the Multidimensional Dyspnoea Profile (MDP) and the Dyspnoea-12 have integrated intensity ratings of sensory quality with affective descriptors [75-77]. The unpleasantness of breathlessness, even when artificially induced in a controlled laboratory setting, is associated with existential fear and reported by subjects as a feeling of impending death [78]. Functional impact measures involve assessment of ways in which breathlessness affects functional performance, employment, quality of life, and psychosocial function [69]. It is measured through a unidimensional rating of disability or activity limitation (mMRC scale [53]) or through unidimensional or multidimensional assessments of quality of life, as in the St. George's Respiratory Questionnaire and the Chronic Respiratory Questionnaire [79, 80].

Sensations (or qualities) of breathlessness include air hunger or unsatisfied inspiration, work/effort, and chest tightness [71, 81, 82]. These sensations vary in intensity and duration and may be evoked by different stimuli with involvement of different afferent pathways [71, 83]. The sensation of air hunger is often described by patients as an uncomfortable urge to breathe and is associated with descriptors such as “I am starved for air” and “I cannot get enough air in” [71]. The work/effort sensation of breathlessness is prevalent in both health and disease, and associated with descriptors like “breathing requires more effort or work” or “breathing is difficult” [71]. The sensation of chest tightness is commonly described as the “chest is constricted” and the “chest feels tight,” which can be induced by bronchoconstriction and is commonly associated with asthma [81].

Epidemiology and impact

In epidemiological studies, breathlessness is commonly measured as activity-related breathlessness using the mMRC scale [53]. In a study by Gronseth *et al.* (n=9500; age >40 years, 15 countries), 27% of subjects were assigned an mMRC score ≥1 (shortness of breath when walking rapidly on level ground or up a slight hill), 13% an mMRC score ≥2 (shortness of breath when walking at own pace on level ground or when walking 100 yards or for a few minutes), and 2% had breathlessness at rest [84]. Chronic breathlessness that limits activity (mMRC score ≥1 for at least three of the previous six months) was reported by 9% of the general population in South Australia [85]. Among COPD patients managed in primary care in the United Kingdom, 38% presented an mMRC score ≥1 with moderate to severe breathlessness (mMRC score ≥2) reported by 44% [86].

Breathlessness is associated with poor clinical outcomes including worse health-related quality of life, increased hospital admissions, and reduced survival [84, 87, 88]. It is a better predictor of five year survival than airway obstruction measured as FEV_1 in COPD [88]. Breathlessness is an unpleasant and frightening symptom with a significant impact on patient psychological state and social life [89, 90]. It is frequently linked to comorbid anxiety and depression, reduced exercise capacity, and quality of life [91, 92]. Breathlessness leads to a vicious cycle of avoidance of physical activity, physical deconditioning, and worsening breathlessness [93]. Breathlessness-related fears related to physical exercise are associated with poorer performance on exercise tests and worse outcome of pulmonary rehabilitation in patients with COPD [94].

Despite its significant impact on patients, chronic breathlessness might be under-recognized. Research has demonstrated a lack of concordance between individuals with COPD and their physicians in perception of breathlessness and its severity, despite breathlessness being identified as the dominant and most distressing symptom by both groups [95]. It is recommended that physicians assess and regularly document patient experiences of breathlessness at clinical interactions [96]. Currently, there is no consensus on how to clinically characterize the quality of breathlessness. However, its assessment should include measures of intensity and associated distress [96]. To highlight the significance of breathlessness, it has been suggested that identification and optimal treatment of chronic breathlessness, similar to pain, should be recognized as a basic human right [97, 98].

Mechanisms

Breathlessness reflects a discrepancy between the demand to breathe (central neural drive) and the ability to breathe (respiratory effort) (Figure 1) [99-101]. The central nervous system directs an outgoing motor command to the respiratory muscles via the phrenic and thoracic spinal nerves. Afferent impulses from mechanoreceptors in airways, lungs, and chest wall and from chemoreceptors are relayed to the brainstem, limbic system, and sensory cortex for integration and central processing [101]. If the afferent feedback is not adequately matched to the outgoing neural respiratory drive, a neuro-mechanical dissociation results in the sensation of breathlessness [102, 103]. There is a conscious awareness of the outgoing motor command to the respiratory muscles attributed to a corollary discharge from the motor cortex and respiratory neurons in the brainstem and transmitted to the somatosensory cortex [101, 104].

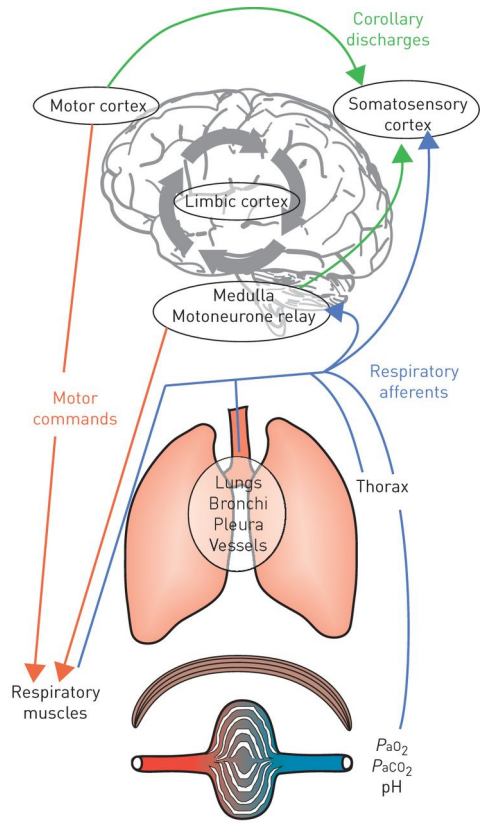


Figure 1. Neurobiological model of breathlessness.
From Laviolette *et al.* [100]. Reproduced with permission of the © ERS 2019.
European Respiratory Journal 2014 43: 1750-1762; DOI: 10.1183/09031936.00092613

The sensation of work/effort is thought to arise from respiratory muscle afferent signals and the awareness of outgoing voluntary cortical motor command, i.e. corollary discharge [71, 101, 105]. In contrast, the source of the air hunger sensation is presumed to be increased chemoreceptor stimulation, by hypoxia or hypercapnia, of brainstem respiratory centers that is not matched by an adequate ventilatory response, i.e. neuro-mechanical dissociation [71, 101].

Our knowledge of the neural processing of breathlessness stems chiefly from parallels in the field of chronic pain and findings of recent neuroimaging studies [106]. Central integration of breathlessness and pain involve similar brain structures [107, 108]. A dual-pathway model is proposed: Ventroposterior thalamic areas and sensorimotor cortices are responsible for the sensorimotor aspects (work/effort) of breathlessness [109-112]. The second pathway involves the medial-dorsal thalamic areas, insula, hippocampus, amygdala, and cingulate cortex, which process the affective qualities (unpleasantness) of breathlessness. The insula has been suggested to be central for emotion-processing and aversive learning [108, 110]. Von Leupoldt *et al.* manipulated breathlessness discomfort by presenting subjects with emotion-evoking images and reported higher degrees of unpleasantness associated with increased brain activity in the amygdala and anterior insula [113]. Low-dose opioids have been reported to significantly reduce the unpleasantness of breathlessness by decreasing the activity of several brain centers, including the insula [114].

Recently a Bayesian model of breathlessness was proposed, in which perception of breathlessness is contingent on a delicate balance between brain predictions or expectations based on past experiences and learned behaviors (priors) and incoming afferent signals (Figure 2) [115, 116]. An individual's priors may be influenced by psychological traits (negative affect, anxiety) that can act as moderators and alter the balance between priors and afferents and potentially exacerbate perception of breathlessness [117, 118]. As this Bayesian system strives for efficiency, it seeks to minimize the differences between prior expectations and afferent sensory information [117]. Priors are generated in a network consisting of the anterior insula, anterior cingulate cortex, orbitofrontal cortex, and ventromedial prefrontal cortex, which are associated with predictions about body state and emotion [119]. Afferent signals are fed into this network via the periaqueductal gray and the posterior insula [118, 120]. Research to increase our understanding of mechanisms of breathlessness is ongoing [117].

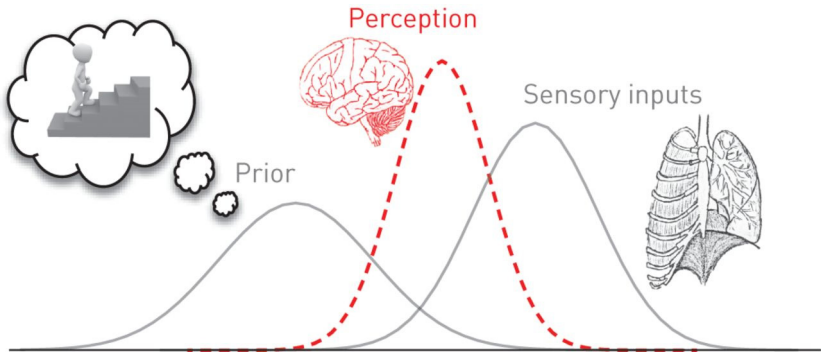


Figure 2. The Bayesian brain hypothesis.
From Faull et al. [115]. Reproduced with permission of the © ERS 2019. European Respiratory Journal 2018 51: 1702238; DOI: 10.1183/13993003.02238-2017

Psychological factors

Contextual and behavioral, along with psychological, factors, particularly negative memories, anxiety, and depression, can affect perception and anticipation of breathlessness [108, 121, 122]. Fearful anticipation of breathlessness leads to a negative spiral of physical activity avoidance, increased physical deconditioning, and deteriorating chronic breathlessness [94, 123, 124]. In healthy individuals, involvement of emotion-related brain areas such as the insula, anterior cingulate cortex, and amygdala during anticipation of breathlessness reflects an amplified affective, primarily fearful, evaluation of impending breathlessness and might underlie avoidance behavior [111]. Increased activation of the hippocampus and amygdala during anticipation of breathlessness has been shown to be closely related to reduced exercise capacity and impaired quality of life as well as to higher levels of breathlessness and anxiety in patients with COPD [125]. Hayen *et al.* observed opioid-induced suppression of activity in the amygdala and the hippocampus during the anticipation period, which correlated positively with reductions in unpleasantness of breathlessness [114]. The authors suggested that, in addition to effects on brainstem respiratory control, opioids might palliate breathlessness by altering associative learning mechanisms [114]. Non-pharmacological interventions could modify psychological and emotional mechanisms involved in perception of breathlessness [126].

Laboratory studies

Mechanisms underpinning exertional breathlessness in COPD have been described in recent years [101, 127-131]. When compared to aged-matched controls, patients with COPD have increased levels of breathlessness at a given level of work, oxygen uptake, and minute ventilation [101, 128]. This results from the inability of tidal volume to expand appropriately with increased ventilation, due to dynamic lung hyperinflation and reduced inspiratory capacity [129]. When the inspiratory reserve

volume reaches its lowest critical value of 0.6 L, further tidal volume expansion is greatly impaired. There is simply "no more space to breathe," and there is a sharp rise in intensity of breathlessness and a change in its quality to “unsatisfied inspiration” [130, 132]. In recent years, with the development of diaphragmatic electromyography, it has been suggested that breathlessness in COPD can be largely explained by an increased awareness of levels of neural respiratory drive [128, 131]. The level of neural respiratory drive to the diaphragm is expressed by quantifying the diaphragm electromyogram (EMGdi) activity as a percentage of maximum (EMGdi%max) [131]. Faisal *et al.* reported that the relationship between intensity of breathlessness and EMGdi%max during exercise was similar in patients with COPD and those with interstitial lung disease, reflecting that disease-specific differences in lung pathology, mechanics, and respiratory muscle activity did not influence the key association between intensity of breathlessness and neural respiratory drive [128].

Epidemiological predictors

Important predictors of prevalence of breathlessness (mMRC ≥1) in the general population include sex, age, smoking status, body mass index (BMI), education level, and lung function measured by spirometry [84, 85]. Breathlessness is reported to be twice as prevalent in females as in males, related to their lower absolute lung volumes and thus lower ventilatory capacity [133-136]. When matched with respect to absolute FEV_1 or FVC, males and females, both healthy and with lung function impairment due to COPD, showed similar likelihood of experiencing breathlessness [137]. Chronic breathlessness is common in older adults and is reported to predict functional decline over 5 years [138]. Several studies report a strong association of high BMI with severe breathlessness [84, 139, 140].

Treatment

Treatment of underlying cause(s) remains the mainstay of therapy for breathlessness. Other strategies involve interventions that (1) reduce the ventilatory demand and the drive to breathe, (2) improve ventilatory capacity, and/or (3) affect central processing. A multidisciplinary approach combining pharmacological and non-pharmacological interventions is recommended by international guidelines (Figure 3) [141-144].

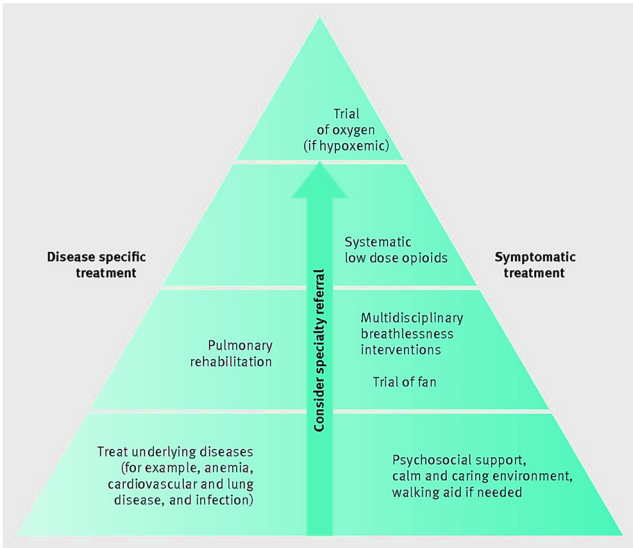


Figure 3. Principles of chronic breathlessness management.
From Ekström *et al*. [145] Reproduced with permission of the © BMJ Publishing Group Ltd 2019.
The BMJ 2015 Jan 2;350:g7617. DOI: 10.1136/bmj.g7617

Non-pharmacological interventions include self-management techniques, walking aids, pulmonary rehabilitation, and multidisciplinary breathlessness services [145-147]. The best known intervention is pulmonary rehabilitation, which improves coping with, and mastery (self-efficacy) of, breathlessness, but the exercise-based programs are poorly implemented and underused in clinical practice [58, 147]. An inexpensive and simple self-management technique is the use of a hand-held powered fan, which been shown to be moderately effective in relieving breathlessness at rest with no adverse effects [148, 149].

Pharmacological evidence-based treatments include supplemental oxygen therapy and systemic opioids [59, 145]. Studies of supplemental oxygen therapy to improve breathlessness in patients with COPD without severe hypoxemia have reported contradicting results [150, 151]. Systemic low-dose opioids have moderate evidence for relief of breathlessness, but many questions remain unanswered [152, 153]. A Cochrane review and meta-analysis of benzodiazepines reported no evidence of a

beneficial effect on breathlessness in COPD [154]. Early studies reported some benefit from systemic antidepressants, but a recent large randomized control trial (RCT) investigating the efficacy of sertraline on breathlessness in COPD found negative results [155].

Oxygen therapy and opioid treatment are reviewed in separate sections of this thesis.

Oxygen therapy for breathlessness

Epidemiology

Since its introduction on a large scale in the mid-1980s, the number of patients starting long-term oxygen therapy (LTOT) for COPD has increased markedly throughout the world [156, 157]. In Sweden, from 1987 through 2015, the incidence of LTOT increased linearly from 3.9 to 14.7 per 100,000 inhabitants, with a national prevalence of 30.6 per 100,000 inhabitants in 2015 [158]. This rising incidence might partly reflect an aging population and reduced mortality from other diseases, chiefly cardiovascular disease. The mean age of patients starting LTOT has increased from 66 to 76 years during the same time period [158]. Airway disease has been the primary indication for prescribing LTOT (69%), with 62% of patients having physician-diagnosed COPD [158]. Adherence to the indication criteria has not decreased, as the baseline mean PaO_2 of 6.5 kPa and the proportion of patients (88%) with severe hypoxia has remained unchanged over time [158].

Surveys across countries have reported that ∼15%–45% of patients on LTOT do not meet the severe hypoxemia criterion, and that many patients on LTOT show moderate hypoxemia [159]. Reliable estimates of the number of prescriptions written for supplemental oxygen for patients with moderate hypoxemia or exercise-induced desaturation are not readily available. Of patients (n=2000) starting supplemental oxygen therapy in 2017 and registered in the Swedevox register, 1000 (50%) were prescribed therapeutic LTOT for severe hypoxemia, 800 (40%) were prescribed palliative oxygen for symptom relief, and 150 (7.5%) because of moderate hypoxemia or exercise-induced desaturation [160]. However, oxygen saturation before initiation of treatment is not reported in Swedevox for palliative and exercise-induced desaturation, making further evaluation difficult [160].

Mechanisms

The beneficial effect of supplemental oxygen therapy on breathlessness might be explained by its ability to restore the mismatch between ventilatory demand and ventilatory capacity. Supplemental oxygen therapy given before or during exercise might increase blood oxygen content and delivery to muscles and thus prolong aerobic metabolism during exercise. This may decrease muscle fatigue and formation of lactic acid, thereby reducing a hypoxemia-related increase in ventilatory drive, dynamic hyperinflation, and increased exertional breathlessness in some patients [161].

Evidence

Long-term oxygen therapy is an established treatment in COPD to improve survival of patients with chronic severe hypoxemia when prescribed for at least 15 hours per day [60, 61]. Based on the inclusion criteria of the Nocturnal Oxygen Therapy Trial and the Medical Research Council trials, the indications for prescribing LTOT are severe resting daytime hypoxemia or moderate hypoxemia together with signs of right-sided heart failure or secondary polycythemia [59].

The effect of LTOT on mortality in moderate hypoxemia has been questioned [150, 151]. Trials investigating the role of supplemental oxygen therapy to improve breathlessness or quality of life in COPD patients with no or mild hypoxemia at rest or during exercise have reported contradicting results.

A Cochrane review of the efficacy of supplemental oxygen for breathlessness in COPD published in 2011 by Uronis *et al*. included a meta-analysis of 18 trials (431 participants) [162]. Supplemental oxygen therapy during exercise reduced breathlessness to a greater extent than did air [162]. A subsequent Cochrane review of 4 trials (331 participants) suggested that longer-term treatment with ambulatory oxygen relieves breathlessness more effectively than air during exercise in people with COPD [163]. Current guidelines do not generally recommend oxygen therapy for COPD patients who do not qualify for LTOT, except as a component of a pulmonary rehabilitation program in patients with exertional desaturation [59, 145].

Several additional studies, including some large trials, have been conducted since the mentioned Cochrane review was published [162], prompting the need for an update of the original review.

Adverse effects

Supplemental oxygen therapy may pose an unnecessary burden and limitations on patients if the treatment is ineffective. Patients report equipment problems and fear of "running out of oxygen" [164, 165]. Being reliant on and connected to oxygen equipment is associated with feelings of embarrassment, restriction of daily activities, and social isolation [164-166]. The use of nasal cannulae can lead to local irritation and nasal drying along with increased risk of nosebleeds [165].

Supplemental oxygen therapy carries a risk of fire incidents and burn injuries, particularly for smokers and those with gas appliances and open fireplaces in the home. The reported incidence of serious burn injuries during supplemental oxygen therapy is low in Sweden because of strict adherence to contraindications and eligibility criteria, including smoking cessation [167].

Treatment with opioids for breathlessness

Mechanisms

The neurophysiological mechanisms of opioid-induced relief of breathlessness are not fully known. It has been suggested that opioids mainly act by reducing neural respiratory drive and/or by altering perception of breathlessness [114, 168-171]. Opioid receptors are abundant in brain centers controlling respiration, including in brainstem and higher centers such as insula, thalamus, and anterior cingulate cortex and are also expressed in chemoreceptors in carotid and aortic bodies and mechanosensory receptors in the airways. The brainstem generates respiratory rhythm and is exquisitely sensitive to opioids [172]. In addition, opioids act on higher cortical centers that provide contextual awareness of respiration leading to top-down modulation of brainstem respiratory control [168].

Opioids produced substantial relief of air hunger with only a small reduction in ventilation in healthy participants in a laboratory setting [170]. In subjects that are awake, morphine has little effect on resting ventilation, but care should be taken in patients with a history of sleep apnea [170]. In a recent randomized crossover trial among COPD patients with chronic breathlessness, single-dose of oral morphine versus placebo improved sub-maximal exertional breathlessness and increased exercise endurance [169]. No changes in cardiac, metabolic, gas exchange, or dynamic operating lung volume responses to exercise were observed. However, small but statistically significant reductions in ventilation and breathing frequency were noted, which were accompanied by reductions in neural inspiratory drive to the diaphragm (EMG di%max) [169]. Taken together, these findings support that

opioids mainly have central effects and reduce central corollary discharge from brainstem respiratory centers to various cortical and sub-cortical regions, which express high densities of opioid receptors [169].

Opioids may also modify neural activity in cortico-limbic brain areas that regulate emotional and memory functions related to anticipation of breathlessness. In a recent neuroimaging study, opioids reduced unpleasantness of breathlessness but not its intensity [114]. The mechanism of action was presumed to be opioid-induced reduction of neural activity in the amygdala and hippocampus during the anticipatory period, regions implicated in aversive memory formation [114]. Reductions in breathlessness unpleasantness also correlated with increased activity in the right anterior cingulate cortex and nucleus accumbens, well-established components of the endogenous opioid system known to decrease the perception of aversive stimuli [114].

Evidence

Since the isolation of morphine from opium in the 19th century by Friedrich Serturner of Germany, opioids have represented the most potent drugs for the relief of severe pain [173]. Beginning in the 21st century, the potential of opioids in symptomatic management of breathlessness has been increasingly recognized. The recent GOLD, European, American, and Canadian clinical practice guidelines recommend systemic low-dose opioids for relief of chronic breathlessness in patients with COPD [141-144].

In 2001, Jennings *et al.* conducted a Cochrane review and meta-analysis of RCTs and concluded that oral or parenteral opioids were beneficial for treatment of breathlessness in terminal illness [174]. This evidence was taken further in a crossover trial in 2003 by Abernethy *et al.*, in which 20 mg daily oral sustained release morphine versus placebo for four days provided significant improvement in breathlessness in participants, 88% of whom were diagnosed with COPD [175]. In 2015, a systematic review and meta-analysis by Ekström *et al.* (15 crossover trials and 1 parallel-group study, 271 participants, 95% with severe COPD), reported that breathlessness was reduced by systemic opioids (eight studies, 118 participants) and less consistently by nebulized opioids (four studies, 82 participants), but found no effect on exercise capacity (13 studies, 149 participants) [152]. The quality of evidence was moderate for systemic opioids and low for nebulized opioids [152]. A recent Cochrane review by Barnes *et al.* reported opioids to show an overall less beneficial effect on breathlessness, despite many similarities and overlapping study populations, but the review exhibited considerable methodological issues [153].

Some randomized trials of morphine have produced negative results. In a trial of 20mg daily extended release morphine versus placebo for 7 days, the primary

endpoint of reduction in intensity of average breathlessness during the final 24 hours was not obtained (published as abstracts) [176, 177]. This may be related to the fact that participants in both groups were allowed to use immediate-release morphine as needed [176, 177]. Patients may also have increased the intensity of physical activity during the trial, thus presenting a breathlessness rating similar to the placebo condition.

Adverse effects

Common adverse effects of opioids such as nausea and constipation require adequate prophylactic treatment when initiating treatment. Some patients experience intolerable nausea and constipation and are not able to continue with opioids. In a pharmacovigilance study, 10mg daily sustained-release oral morphine was increased in non-responders by 10mg per day in seven day increments to a maximum of 30 mg [178]. The maximum dose of 30mg led to withdrawal of 15 of 83 patients because of unacceptable side effects, including drowsiness, confusion, and constipation [178]. All adverse reactions rapidly reversed when morphine was discontinued and none resulted in hospitalization. There was no evidence of tolerance in up to 22 months of follow-up [178].

It is unclear if COPD treatment with opioids increases hospitalizations and/or mortality. Observational population-based studies have reported conflicting findings regarding increased morbidity and mortality associated with opioids. In a large observational study in Canada, new opioid prescriptions for COPD patients were associated with a significant increase in 30-day mortality and emergency room visits [179]. Palliative care patients who would be mainly prescribed opioids for breathlessness were excluded from the study. The indications for opioid prescription and the dosage were unavailable, and it is likely that the overwhelming majority were prescribed opioids for pain and not for breathlessness [179]. A large prospective national study of patients with oxygen-dependent COPD in Sweden reported no increased risk of hospitalization or mortality associated with low-dose opioids (<30mg oral morphine equivalents/day) over a four year follow-up [180]. However, respiratory specific outcomes were not determined and the indications were unknown.

Fear of respiratory depression is one of the main reasons for physicians to withhold opioid treatment for breathlessness [181, 182]. In laboratory trials, reductions in ventilation and breathing frequency were observed, but effects were modest and no opioid-related adverse effects on gas exchange parameters were seen [169, 170, 183, 184]. In a recent systematic review and meta-analysis, Verberkt *et al.* [185] found no evidence of significant or clinically relevant adverse respiratory effects of opioids for chronic breathlessness in COPD. However, the included studies were small, of low quality and short duration, and thus underpowered to assess adverse

respiratory effects. Respiratory depression was not assessed in more than half of the studies, and, in the 25 studies that included that outcome, only 11 stated a definition with eight studies using decrease in oxygen saturation as part of the definition and only four studies including increase of $PaCO_2$ [185]. The authors of the review identified the need for a common respiratory outcome to be established for all future trials of opioid therapy for breathlessness in order to conduct a more robust synthesis [185].

Aims

The overall aim of this research was to study the prevalence, management, and pharmacologic treatment of breathlessness in people with severe COPD.

The aims of individual studies were as follows.

Study I

To evaluate the prevalence of symptoms and their management at the end of life in patients with oxygen-dependent COPD in Sweden, compared to those with cancer.

Study II

To quantify the reported indications for opioid prescriptions in oxygen-dependent COPD in Sweden.

Study III

To investigate the efficacy of supplemental oxygen therapy for breathlessness in COPD patients with no or mild hypoxemia.

Study IV

To assess recognition and treatment of chronic breathlessness as compared to chronic pain by physicians in Sweden, using a case-based survey.

Materials and methods

Data sources

The national healthcare and population registries utilized in Studies I and II are described briefly.

The Swedevox Register

The Swedevox register includes prospective data of patients prescribed LTOT since 1987. Swedevox is integrated into routine clinical workflow and provides a national structure for valid prescription and management of LTOT [158]. All clinical units (currently 48) prescribing LTOT in Sweden report to Swedevox. The register has had stable national completeness of 85% since its inception [158].

Swedevox contains baseline data from initiation of LTOT on resting arterial blood gas tension of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) when breathing air and during oxygen therapy, forced expiratory volume in one second (FEV_1), body mass index (BMI), smoking history, World Health Organization (WHO) performance status, and prescribed flow (l/min) and duration (h/day) of LTOT [158]. Patients prescribed only LTOT without palliative oxygen or ambulatory oxygen therapy for COPD were included in these studies.

The Swedish Register of Palliative Care

The Swedish Register of Palliative Care (SRPC) collects data about EOL care of patients regardless of place of care or diagnosis [186, 187]. In 2013, 87% of all cancer deaths nationwide were included in the register [188]. Data are collected through an EOL questionnaire with respect to the presence of breathlessness, pain, death rattle, nausea, anxiety, and confusion during the final seven days of life; the prevalence of unrelieved symptoms during this time; and the prescribing of medications ‘as needed’ for pain, nausea, anxiety, and death rattle at least one day before death (see Paper I supplement for EOL questionnaire) [186].

The EOL questionnaire is completed retrospectively, usually by the responsible nurse within a week of the patient’s death. The report is based on the patient medical

records and recall, preferably after a team discussion so as to include the experience of all team members [186]. A study has supported the validity of the data collection approach [189].

The Swedish Causes of Death Register

The Swedish Causes of Death Register contains information from death records of all deceased registered residents of Sweden since 1952 and is electronically available [190]. The Swedish National Board of Health and Welfare has been responsible for the register since 1994. Causes of death are recorded according to the contemporaneous version of the International Classification of Disease (ICD) [191, 192].

Data include the Swedish personal identity number, age, sex, nationality, marital status, date and country of birth, date of death, place of death (home, hospital, nursing home, or other), underlying cause of death, contributing causes of death, and whether an autopsy was performed [190, 193]. The date and causes of death are stated on a standardized death certificate by the patient's usual physician or the physician confirming the death and sent to the National Board of Health and Welfare within 3 weeks of death. The death certificates are sometimes sent back to the responsible physician for correction [193].

The underlying cause of death is defined by WHO as "the disease or injury that initiated the train of morbid events leading directly to death." In 2015, the underlying cause of death was missing in 0.9% of all deaths in Sweden [190]. The free text diagnoses are coded and checked using computerized algorithms, and the underlying cause of death is selected according to rules from the WHO [194].

The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register includes individual-level data on dispensed prescription drugs in Sweden since July 1, 2005 [195, 196]. The register includes all medications dispensed in outpatient care, but not medications given in hospitals or over-the-counter medications [195]. Registered data for each individual drug dispensed includes the Swedish personal identity number of the patient, information about the prescriber's profession and practice, date of the prescription and the date dispensed, identification of the drug according to the Anatomical Therapeutic Chemical (ATC) classification system, the defined daily dose, the number of packages and permitted refills, cost, and the indications, entered in free-text only [195-197].

Design and analyses

Study I

Design

Patients identified in the Swedevox register as starting LTOT for COPD who died in the time period from January 1, 2011 through October 14, 2013 were included. The physiological data of patients with COPD at time of initiation of LTOT from Swedevox were cross-linked with SRPC data of prevalence of symptoms, degree of symptom relief, and symptomatic treatment during the final seven days of life using each patient's unique Swedish personal identity number. Patients in SRPC who died from cancer during the same time period were included as a comparison group. A sub-analysis including only those patients with lung cancer as the comparator group was also carried out.

Assessment

We recorded prevalence of all symptoms listed in the question of the EOL questionnaire "Were any of the following symptoms prevalent at some time during the final week of life?" (yes or no). For each reported symptom, the level of symptom relief was graded as relieved, partially relieved, or unrelieved. Prevalence of as-needed medication prescriptions was analyzed among symptomatic patients for each identified symptom according to the question "Was medication prescribed for use 'as needed' in the form of injections before death for pain, death rattle, nausea, or anxiety?" (yes or no).

Endpoints

The primary endpoint was the prevalence of symptoms during the final seven days of life in COPD patients as compared to cancer patients. Secondary outcomes included comparison of EOL care, prevalence of unrelieved symptoms, and prevalence of as-needed medication prescriptions in COPD and cancer.

Ethics

The study was approved by the Regional Ethics Review Board of Lund University (LundDNr 2013/379).

Statistical methods

Baseline characteristics were summarized using standard descriptive statistics. Differences between groups were tested using t-test for continuous variables and chi-square test for categorical variables. Significance was defined as a double-sided

$p < 0.05$. Statistical analyses were conducted using the software package Stata, version 12 (StataCorp LP; College Station, TX, USA).

Study II

Design

Patients reported in the Swedevox register as beginning LTOT for COPD from October 1, 2005 through June 30, 2009 were included in the study. Data of all dispensed outpatient prescriptions were obtained from the Swedish Prescribed Drug Register during the study period, which extended from 91 days prior to initiation of LTOT until LTOT withdrawal, death, or the conclusion of the study on December 31, 2009. Drugs were categorized according to ATC codes. Vital status were obtained from the Swedish Causes of Death Register.

Assessments

A random sample (n=2,000) of the opioid prescriptions dispensed during the study period was analyzed. Data of medication type, quantity dispensed, and date of dispensing were analyzed, with indications reviewed by a respiratory physician (EB) and categorized as pain, breathlessness, other, or unknown based on the indication in the free-text field. A given prescription may have had multiple indications and potentially include both a regular and an "as-needed" dose. In Sweden, the stated free-text indications are decided entirely by the prescribing physician and do not undergo external review by the pharmacy or clinic.

Endpoints

The primary endpoint was the study period prevalence of, and indications for, opioids dispensed to people with end-stage COPD.

Ethics

Participants provided verbal consent for their data to be accessed for research purposes when registered in Swedevox, with the consent procedure and this study approved by the Regional Ethics Review Board of Lund University (157/2007 and 350/2008). The Swedevox register was approved by the Swedish National Board of Health and Welfare and the Data Inspection Board when it was established.

Statistical methods

Statistical methods included standard descriptive statistics, t-tests, and chi-square tests as appropriate using the statistical package Stata version 13 (StataCorp LP, College Station, TX, USA).

Study III

Design

This was a Cochrane systematic review and meta-analysis of RCTs of the efficacy of supplemental oxygen therapy versus air in non-hypoxemic or mildly hypoxemic patients with COPD who did not qualify for LTOT.

Study selection

A systematic literature search in the databases of the Cochrane Airways Group Register, the Cochrane Central Register of Controlled Trials, MEDLINE, and Embase was conducted. Randomized controlled trials published through July 12, 2016 were included. Inclusion criteria were (1) RCT; (2) participants 18 years of age or older; (3) at least one participant with COPD; (4) mean PaO_2 >7.3 kPa at baseline; (5) no participant receiving LTOT; (6) comparison of oxygen versus air at any dose delivered through a non-invasive method; and (7) endpoints of breathlessness or health-related quality of life (HRQOL). Studies of oxygen therapy versus air delivered through nasal prongs or mask during exertion, continuously, as needed over a defined period, or as short-burst oxygen before exertion were included. Two review authors (ME and ZA) independently assessed articles for inclusion and collected data.

Endpoints

The primary endpoint was the level of breathlessness measured on any validated scale. Secondary endpoints included HRQOL measured on any validated scale, blinded participant preference to continue therapy, and adverse events.

Quality assessment

The risk of bias was assessed using the Cochrane Risk of Bias Tool. Two review authors independently assessed each study for risk of bias in allocation sequence generation, allocation concealment, blinding of participants and outcome assessors, handling of missing data, selective outcome reporting, and other potential threats to the validity of studies in line with recommendations provided in the Cochrane Handbook for Systematic Reviews of Interventions [198]. We conducted a retrospective risk of bias assessment using the above method for all studies included in the review published in 2011 [162].

Statistical methods

Effect estimates measured on different scales were standardized by dividing each mean difference with its standard deviation (SD), providing standardized mean differences (SMD). Effect sizes were reported as SMD with 95% confidence intervals (CI) using random-effects models in Revman 5 (Cochrane Informatics and

Knowledge Management, Oxford, UK). Lower SMDs indicated decreased breathlessness. Sub-analyses and sensitivity analyses were performed, and the quality of evidence was assessed according to the Grading of Recommendations, Assessment, Development, and Evaluations approach.

Study IV

Design

Study IV was a double-blind, randomized (1:1), controlled, parallel-group, web-based trial using hypothetical case scenarios. Swedish physicians managing patients with respiratory symptoms were randomized (1:1) to a case scenario of a patient with optimally treated COPD, with either severe chronic breathlessness or severe pain that markedly restricted daily activities.

Recruitment

Recruitment procedures were pre-specified in the protocol: study information and a link to the survey were emailed to physicians with membership in the Swedish Respiratory Society, the Swedish Society of Internal Medicine, the Swedish Society of Primary Care, the Swedish Society of Palliative Medicine, and at the authors' departments (internal medicine, pulmonary medicine, and primary care). The study was publicized in journals of the professional associations. Study data were not reviewed or analyzed prior to trial closure.

Eligibility and characteristics

After being informed that this was an anonymous survey on management in clinical practice of a patient with respiratory problems, participants meeting the eligibility criteria were asked to consent to participate. Inclusion criteria were licensed physician; treating patients with respiratory problems in clinical practice; able to read and understand a case description written in Swedish; not on the research team or aware of the study design or content; and no previous participation in the study. The participants logged into a website using their Swedish personal identity number to avoid entry more than once. Date of birth was stored encrypted in a separate database with no connection to the survey answers and was not available to those analyzing the survey. Data were collected on the participant's age, gender, professional seniority, present location of practice, specialty license(s), current specialty area(s) of practice, and number of years as a practicing physician (see Paper IV supplement).

Randomization and case scenario

Eligible participants were randomized to a case scenario with either chronic breathlessness or chronic pain. The participants were not aware of the randomization or the purpose of the trial. The hypothetical case scenario was constructed based on the investigators' clinical experience to reflect a patient diagnosed with severe COPD optimally treated with triple inhalation therapy, vaccination against influenza and Pneumococcus, and individualized pulmonary rehabilitation training according to GOLD guidelines [199].

The patient in the case was troubled by (randomized) either severe chronic breathlessness or chronic pain restricting daily activities that had remained unchanged for at least three months. The patient's gender was also randomized but not analyzed in the study. All other details of the case scenarios were identical. The clarity, consistency, face validity, and clinical plausibility of the case scenarios and study questions were tested on a sample of physicians (n=10) who did not subsequently participate in the survey and were modified accordingly. The case scenario and all questions are available in Paper IV supplement.

The case progressively revealed more information with associated questions regarding how the physicians would care for the patient in terms of diagnostic procedures and treatment options. The study participants chose from a list of tests and treatments at each stage. The participant was required to answer each question in order to advance to the next page, and each page was saved separately before proceeding. The participant could not return to or change earlier responses.

Endpoints

The study endpoints were assessed in four stages: (1) further treatment; (2) symptomatic treatment; (3) treatment with opioids; and (4) when applicable, reasons for not treating with opioids. Through this stepwise process, participants were required to actively respond at each stage according to what they would do in their clinical practice without being reminded of all potential management options available. At the end of the survey, all participants were informed that the patient had breathlessness with an intensity of 7/10, and the proportion of physicians that considered the described breathlessness to be chronic was assessed. The physicians were also asked whether they prescribed opioids for breathlessness versus for pain in their actual clinical practice, and the respective proportions were calculated.

Ethics

The study was approved by Regional Ethics Review Board of Lund University (Dnr: 2015/596) and prospectively registered with ClinicalTrials.gov (NCT02728674). All participants provided informed consent.

Statistical methods

The endpoints were compared between groups using chi square tests and multivariable logistic regression presented as odds ratios (OR) with 95% CI, adjusted for physician seniority (resident or consultant) and current specialty (internal medicine, primary care, pulmonary medicine, or other). Statistical significance was defined as a two-tailed $p < 0.025$ due to two co-primary endpoints. Analyses were performed using Stata version 14.2 (StataCorp LP; College Station, TX).

Sample size

The protocol specified a preliminary sample size of 182 physicians to provide 80% power to detect a difference of 20% in the primary endpoint of need for symptomatic treatment. In the absence of prior data, we assumed that 60% would continue with further treatment for chronic breathlessness and 80% for chronic pain and calculated a false positive risk (alpha) of 0.05 in a 2-sided test. After the pre-defined recruitment procedures, the study was closed, with 134 participants completing the study. Given the final proportions of 10% versus 30% for identifying the need for further symptomatic treatment, a sample size of 114 participants (57 per group) was needed to obtain at least 80% power for the primary analysis. For the actual sample size of 134 participants, the power for detecting the observed between-group difference in primary analysis was 86%.

Results

Study I

In total, 1,128 COPD patients (mean ± SD age 78±8 years at death; 60% female) and 56,843 cancer patients (age 75±12 years at death; 49% female) were included in the study (Figure 4) [200]. Of the LTOT patients recorded in Swedevox, 59% were also registered in the SRPC and included in the study. Characteristics with respect to age, sex, lung function, body mass index, and arterial blood gas levels in LTOT patients who were included in the study and those not in the SPRC, and thus not included, were similar, supporting its external validity (Table 1).

Death was expected in 80% of COPD patients and 95% of cancer patients (Table 2). The COPD patients more often died in hospital (49% vs 28%) and received less specialized palliative home care (4% vs 14%). Fewer COPD patients had an EOL discussion (33% vs 61%) ($p < 0.001$ for all comparisons). Validated symptom scales were used less frequently in COPD patients than in cancer patients for pain (12% vs 28%, $p < 0.001$) and for other symptoms (8% vs 15%, $p = 0.004$).

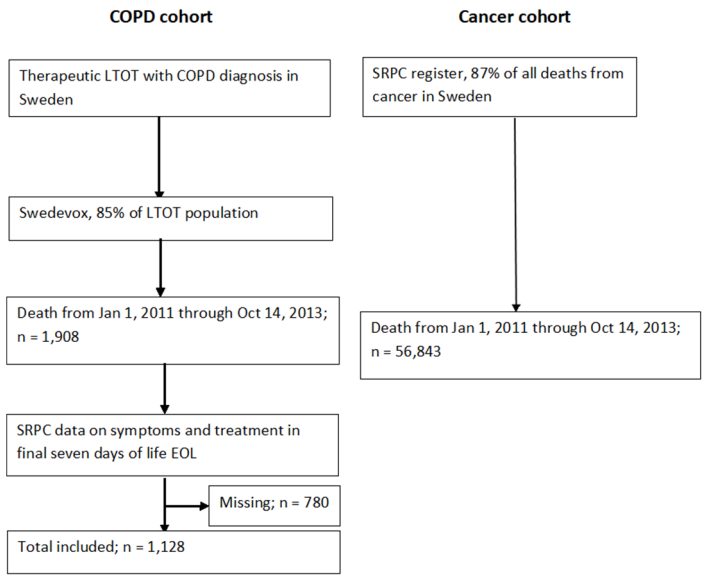


Figure 4. Study Design.

Table 1. Characteristics of COPD patients with LTOT dying from January 1, 2011 through October 14, 2013 registered in SRPC (study patients) and those not registered in SRPC.

Characteristic	COPD included in SRPC, n=1,128	COPD, not registered in SRPC, n=780
Age, years (at death)	77.8 ± 8	77.5± 8
Female, n (%)	680 (60)	440 (56)
FEV_1, L	0.83 ± 0.5	0.88± 0.5
FEV_1 % pred*	32 (23-45)	32 (24-47)
BMI, kg/m^2	23.4 ± 6.1	24.2 ± 6.5
PaO_2 breathing air, kPa	6.6 ± 0.85	6.5 ± 0.87
$PaCO_2$ breathing air, kPa	6.2 ± 1.2	6.2 ± 1.3

Data presented as mean ± SD unless otherwise specified. *Median (first quartile – third quartile). FEV_1=forced expiratory volume in one second; BMI=Body mass index; PaO_2=arterial blood gas tension of oxygen on breathing air; $PaCO_2$=arterial blood gas tension of carbon dioxide on breathing air.

Table 2. EOL care in patients with oxygen-dependent COPD, cancer and lung cancer.

	COPD n = 1,128	Cancer n = 56,843	Lung cancer n = 10,822
Age, years at death	77.8 ± 8	75.2 ± 12	72.9 ± 10
Female, n (%)	680 (60)	27,573 (49)	5,233 (48)
End of life discussion with patient, n (%)	372 (33)	34,916 (61)	6,337 (59)
End of life discussion with family, n (%)	593 (53)	43,046 (76)	7,923 (73)
Optional care facility	378 (34)	31,188 (55)	5,166 (48)
Place of death, n (%)			
- Hospice/palliative hospital ward	81 (7)	14,311 (25)	2,988 (27)
- Hospital ward, not palliative	553 (49)	15,735 (28)	3,964 (37)
- Nursing home†	268 (24)	8,303 (15)	746 (7)
- Specialized palliative home care	48 (4)	8,154 (14)	1,421 (13)
- Home care, "basal"	78 (7)	3,683 (7)	529 (5)
- Short-term care home	88 (8)	6,339 (11)	1,108 (10)
- Other	12 (1)	317 (1)	66 (1)
Expected death, n (%)			
- Unexpected†	172 (15)	2,065 (4)	454 (4)
- Expected†	902 (80)	53,898 (95)	10,205 (94)
- Unknown	54 (5)	880 (1)	163 (2)
Use of validated symptom scale for pain	134 (12)	16,160 (28)	3,024 (28)
Use of validated symptom scale for other symptoms	86 (8)	8,365 (15)	1,518 (14)

Compared to patients with cancer, COPD patients suffered from more breathlessness (73% vs 22%) and anxiety (63% vs 54%) but less pain (52% vs 81%) and nausea (11% vs 23%) during the last week of life (Figure 5a). COPD patients had lower rates of total relief from breathlessness (22% vs 37%), anxiety (52% vs 61%), and death rattle (33% vs 44%) than cancer patients (Figure 5b) (p <0.001 for all comparisons).

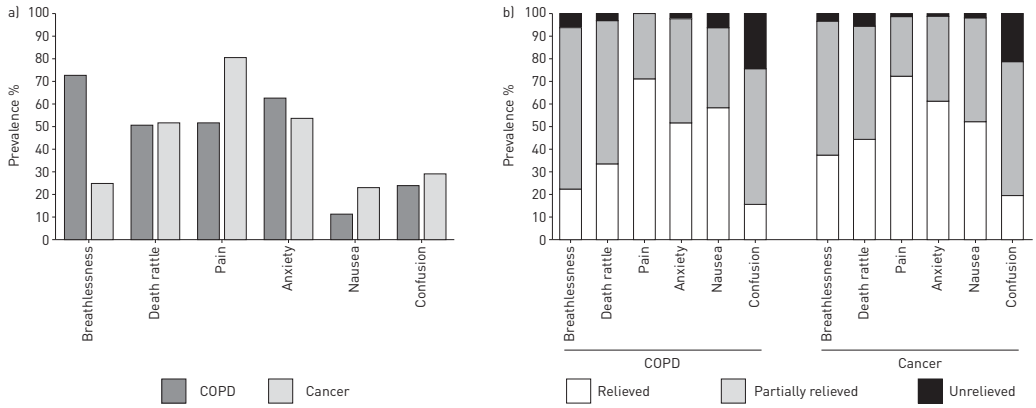


Figure 5. Patients with oxygen-dependent COPD (n=1,128) or cancer (n=56,843). The prevalence of a) symptoms, and b) relieved, partially relieved, and unrelieved symptoms in symptomatic patients during the last week of life in Sweden.

Prescription of as-needed medications during the last week of life was significantly lower in COPD than cancer for all symptoms: anxiety (76% vs 89%), death rattle (75% vs 88%), pain (80% vs 96%), and nausea (46% vs 77%) (p <0.001 for all comparisons). In addition, COPD patients were prescribed fewer as-needed medications to address specific symptoms for anxiety (82% vs 95%), death rattle (89% vs 95%), pain (93% vs 97%), and nausea (64% vs 89%) (p <0.001 for all comparisons).

We compared reported EOL care and symptom prevalence among patients with COPD to patients with lung cancer. COPD patients received less EOL care and had limited access to specialized palliative care services than did patients with lung cancer (Table 1). COPD patients experienced more breathlessness than lung cancer patients (73% vs 42%) and had similar levels of anxiety (63%), but pain (52% in COPD vs 73% in lung cancer), death rattle (51% vs 63%), nausea (11% vs 16%), and confusion (24% vs 32%) were more prevalent in lung cancer in the final week of life (p <0.001 for all comparisons except anxiety).

Study II

A total of 2,249 oxygen-dependent COPD patients (59% female) were included prospectively and followed-up for a median 1.1 years (IQR 0.6–2.0) [201]. During the study period, 1,034 patients (46%) were dispensed at least one opioid prescription (13,722 total). Characteristics of patients who were prescribed opioids are shown in Table 4. Mean patient age was 74 years; 66% were female, and 70% presented a WHO performance status of 1–2 at initiation of LTOT. A random sample of 2,000 (15%) of the opioid prescriptions was dispensed to 575 patients with the indication provided in 33% of prescriptions. Characteristics of patients with known indications for opioids were similar to those with unknown indications (Table 3).

Table 3. Characteristics of oxygen-dependent COPD patients prescribed opioids.

Characteristics	Total (n=1,034)	Patients with known indication for prescription (n=273)	Patients with unknown indication for prescription (n=302)
Age (years)	74.6 ± 8	72.7 ± 8	75.9 ± 8
Female, n (%)	684 (66)	188 (69)	217 (72)
PaO_2 air (kPa)	6.6 ± 0.87	6.7 ± 0.86	6.4 ± 0.86
$PaCO_2$ air (kPa)	6.3 ± 1.2	6.3 ± 1.1	6.4 ± 1.2
WHO status, n (%)			
0	49 (5)	17 (6)	11 (4)
1	379 (37)	114 (42)	84 (28)
2	344 (33)	85 (31)	110 (36)
3	145 (14)	22 (8)	56 (18)
4	20 (2)	1 (0)	8 (3)
FEV_1 (L)	0.83 ± 0.5	0.86 ± 0.5	0.80 ± 0.5
FEV_1 (% of predicted)	34 ± 17.3	34 ± 17.9	33 ± 15.4
Follow-up, days*	442 (231 – 754)	568 (262 – 834)	545 (268 – 749)

Data presented as mean ± SD unless otherwise stated. N (%) of missing information of PaO_2, 146 (14); $PaCO_2$, 151 (15); WHO status, 97 (9); FEV_1, 403 (39); FEV_1 (% of predicted), 453 (44). *Median (first quartile – third quartile). FEV_1=forced expiratory volume in one second; PaO_2=arterial blood gas tension of oxygen on breathing air; $PaCO_2$=arterial blood gas tension of carbon dioxide on breathing air; WHO=World Health Organization.

The most commonly dispensed opioids were tramadol (23%), oxycodone (23%), morphine (16%), and codeine (16%) (Table 4). The average dispensed quantity was 9.3 (IQR 3.7–16.7) defined daily doses per prescription. Of the opioid prescriptions, 417 (21%) included an as-needed dose (Table 4).

Table 4. Opioid Prescriptions in Oxygen-Dependent COPD.

Prescriptions	Random sample N=2,000
Substance, n (%)	
Codeine	318 (16)
Dextropropoxifen	270 (14)
Fentanyl	99 (5)
Morphine	314 (16)
Oxycodone	449 (23)
Tramadol	459 (23)
Others	91 (4)
DDDs per prescription*	9.3 (3.7-16.7)
Included 'as needed' dose, n (%)	417 (21)
Indication(s), n (%)	
Pain	642 (32)
Breathlessness	13 (0.7)
Other	7 (0.3)
Unknown	1,338 (67)

A random sample of 2,000 (15%) of the total 13,722 opioid prescriptions were analyzed regarding medication type, dispensed quantity, and indication (free-text). Percentages may not total 100 due to rounding. *Median (first quartile – third quartile). DD=defined daily dose.

Table 5 shows indications for dispensed opioid prescriptions before and after the start of LTOT. In the prescriptions with known indications, the vast majority of the stated indications were pain (97%) with only 2% for breathlessness and 1% for other reasons. Prescriptions with dual indications (pain and breathlessness) occurred in only five (0.7%) of the known indications.

Table 5. Indications of 2,000 random opioid prescriptions among 575 patients with oxygen-dependent COPD.

Indication, n (%)	Overall	6 month period prior to LTOT	First 6 months of LTOT	Final 6 months of LTOT
Known indication	662 (33)	153 (39)	188 (37)	215 (30)
Pain	642 (97)	150 (98)	183 (97)	206 (96)
Breathlessness	13 (2)	1 (0.7)	4 (2)	6 (3)
Other	7 (1)	2 (1)	1 (0.5)	3 (1)
Unknown indication	1338 (67)	236 (61)	325 (63)	508 (70)

Percentages may not total 100 due to rounding.

During the final 6 months of the patient's life, the period prevalence of opioid prescriptions for breathlessness was 4% (Table 6). Opioids were prescribed predominantly to patients with WHO performance status 1−2 (Table 7).

Table 6. Opioids prescribed at LTOT initiation versus prior to death in oxygen-dependent COPD patients who died (n=278).

Indication, n (%)	First 6 months of LTOT	Final 6 months of life
Known indication	75 (28)	106 (29)
Pain	71 (95)	101 (95)
Breathlessness	3 (4)	4 (4)
Other	1 (1)	1 (1)
Unknown indication	191 (72)	265 (71)

Table 7. Indications of opioid prescriptions with respect to WHO performance status in oxygen-dependent COPD.

Indication, n (%)	WHO status 0	WHO status 1	WHO status 2	WHO status 3	WHO status 4
Known indication	38 (45)	273 (42)	224 (32)	55 (17)	2 (7)
Pain	38 (100)	269 (99)	211 (94)	53 (96)	2 (100)
Breathlessness	0	2 (0.7)	8 (4)	2 (4)	0
Other	0	2 (0.7)	5 (2)	0	0
Unknown indication	47 (55)	374 (58)	485 (68)	275 (83)	28 (93)

Percentages may not total 100 because of rounding.

Figure 6 shows the temporal pattern of opioid prescriptions during follow-up with respect to indication. Pain was the predominant indication throughout the study period. The rate of breathlessness as indication increased slightly during follow-up, but absolute numbers remained low.

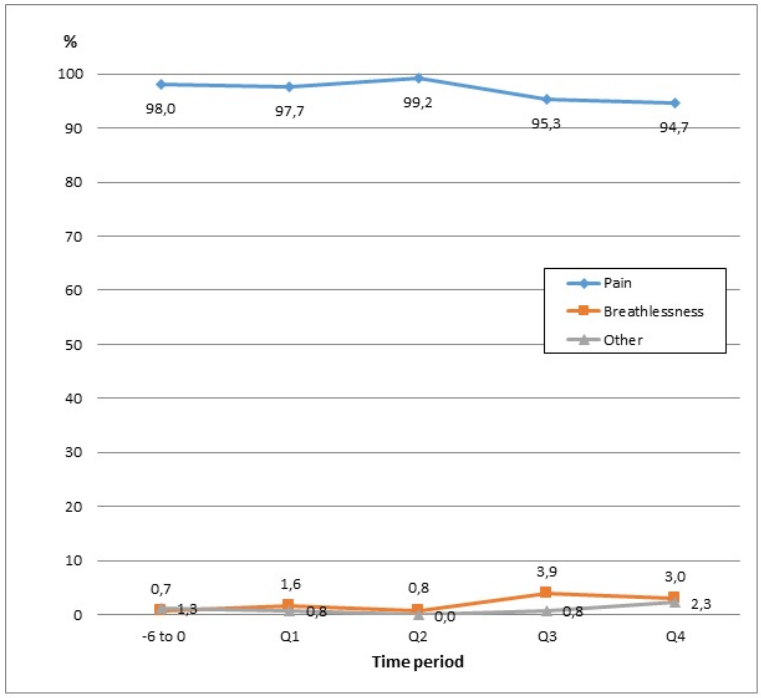


Figure 6. Temporal pattern of opioid prescription during follow-up relative to indication.
Pain was the predominant indication throughout the study period. Breathlessness as an indication increased slightly during follow-up, but absolute numbers remained low. Q=quartile.

Study III

Forty-four studies comprising 1195 participants met the inclusion criteria and were included in this review [202]. Compared with the review published in 2011 [162], we included 14 additional studies (493 participants), excluded one study, and included novel data on HRQOL. We included 33 of the studies (901 participants) in the meta-analysis.

Study characteristics

All studies included participants with COPD and compared supplemental oxygen therapy versus air delivered via the same noninvasive method in both groups. Of the 44 studies, 31 were blind randomized crossover trials and 13 were randomized controlled parallel arm trials. The most frequent mode of administration was the nasal cannula (22 studies), followed by mouthpiece/valve (13 studies), and mask (8 studies). Doses of oxygen provided ranged from 2 to 6 L/min via nasal cannula, and fraction of inspired oxygen (FiO_2) ranged from 24 to 75% via mask/mouthpiece. Thirty-two studies provided continuous oxygen during exercise using a six-minute walk test, endurance shuttle walk test, incremental shuttle walk test, step test, or cycle exercise test. Six studies provided domiciliary oxygen during daily life and activities. Four studies gave participants short-burst oxygen therapy before exertion.

Treatment efficacy

We found that breathlessness during exercise and daily activities was reduced by oxygen compared with air in patients with COPD who did not qualify for LTOT (32 studies; 865 participants; SMD -0.34, 95% CI -0.48 – -0.21; I^2=37%; low-quality evidence). This translates to a decrease in breathlessness of about 0.7 points on a 0 to 10 numerical rating scale. In contrast, we found no effect of short-burst oxygen given before exercise (four studies; 90 participants; SMD 0.01, 95% CI -0.26 – 0.28; I^2 = 0%; low-quality evidence).

Supplemental oxygen therapy reduced breathlessness during exercise trials (25 studies; 442 participants; SMD -0.34, 95% CI -0.46 – -0.22; I^2 = 29%; moderate-quality evidence). Evidence of an effect on breathlessness during daily life activity was limited (two studies; 274 participants; SMD -0.13, 95% CI, -0.37 – 0.11; I^2=0%; low-quality evidence) (Figure 7). Supplemental oxygen therapy did not clearly affect HRQOL (five studies; 267 participants; SMD 0.10, 95% CI -0.06 – 0.26; I^2=0%; low-quality evidence). Patient preference and adverse events could not be analyzed owing to insufficient data.

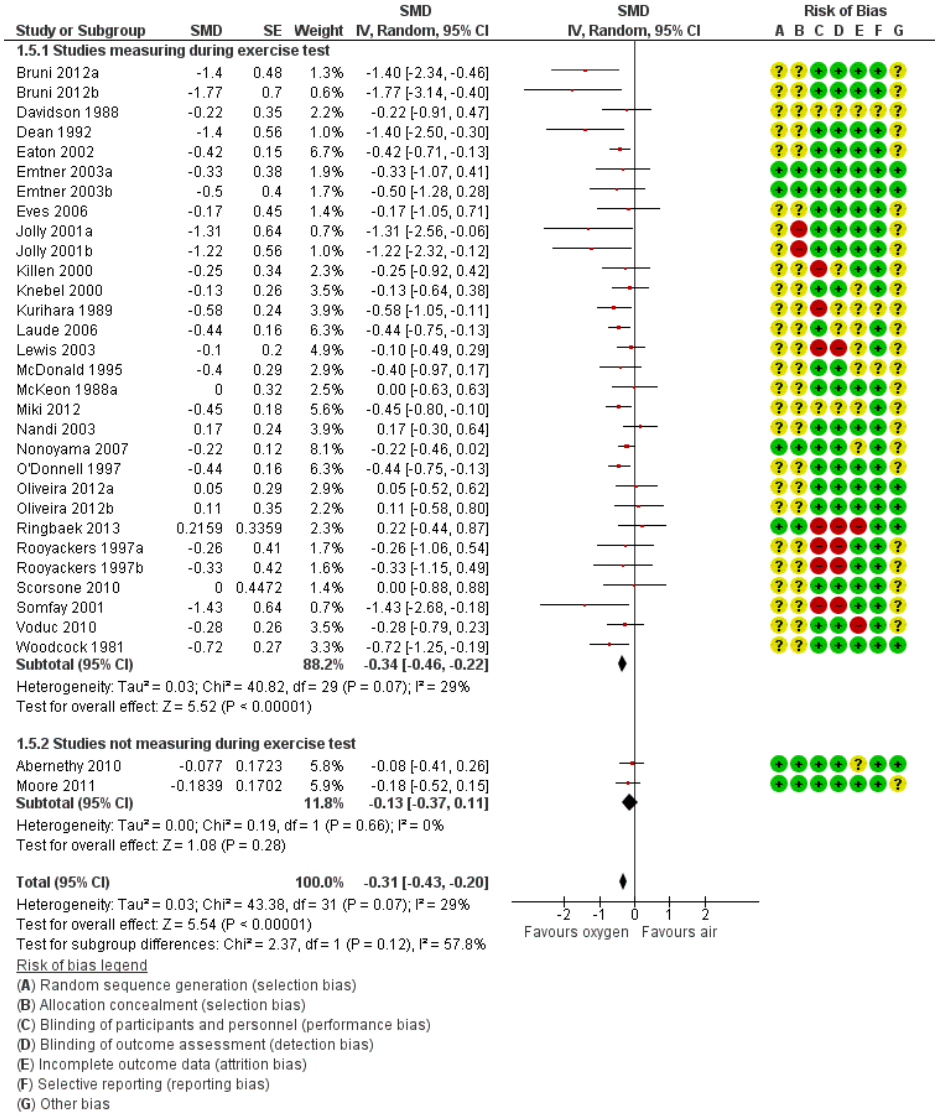


Figure 7. Forest plot of oxygen versus air, outcome of breathlessness; subgroup analysis evaluation during exercise test versus during daily activity.

Study IV

From September 2016 through May 2017, 134 physicians were randomized to a case with chronic breathlessness (n=72) or chronic pain (n=62; Figure 8) [203]. Characteristics of the groups were well balanced; median age 42 years; 53% male; 52% worked in hospital and 46% in primary care; mean years as a practicing physician was 11 (Table 8).

Table 8. Characteristics of participating physicians.

Characteristics, n (%)	All n=134	Breathlessness n=72	Pain n=62
Age, median years (IQR)	42 (35, 56)	44 (35, 56)	40 (35, 51)
Female	63 (47)	34 (47)	29 (47)
Professional seniority			
- Resident	44 (33)	26 (36)	18 (29)
- Specialist	52 (39)	28 (39)	24 (39)
- Senior specialist	38 (28)	18 (25)	20 (32)
Present location of practice*			
- Hospital	69 (52)	36 (50)	33 (53)
- Primary health care	62 (46)	34 (47)	28 (45)
- Other	6 (4)	2 (3)	4 (6)
Specialty license(s)*			
- Internal medicine	50 (37)	23 (32)	27 (44)
- Family medicine	62 (46)	35 (49)	27 (44)
- Respiratory medicine	32 (24)	22 (31)	10 (16)
- Other	28 (20)	11 (15)	17 (27)
Current specialty area(s) of practice*			
- Internal medicine	36 (27)	14 (20)	22 (35)
- Primary care	61 (46)	34 (47)	27 (44)
- Respiratory medicine	32 (24)	22 (31)	10 (16)
- Other	24 (18)	9 (13)	15 (24)
Total work experience as physician, median years (IQR)	11 (5, 22)	11 (5, 24)	12 (6, 20)

Data presented as frequency (percentage) unless otherwise specified. * Percentages may exceed hundred due to overlap. IQR=interquartile range.

In a hypothetical case of chronic breathlessness compared to chronic pain, significantly fewer physicians recognized a need for further treatment (10% vs 31%; p=0.002); fewer offered symptomatic treatment (4% vs 24%; <0.001); and fewer offered treatment with opioids (3% vs 23%; p <0.001) (Figure 8; Table 9).

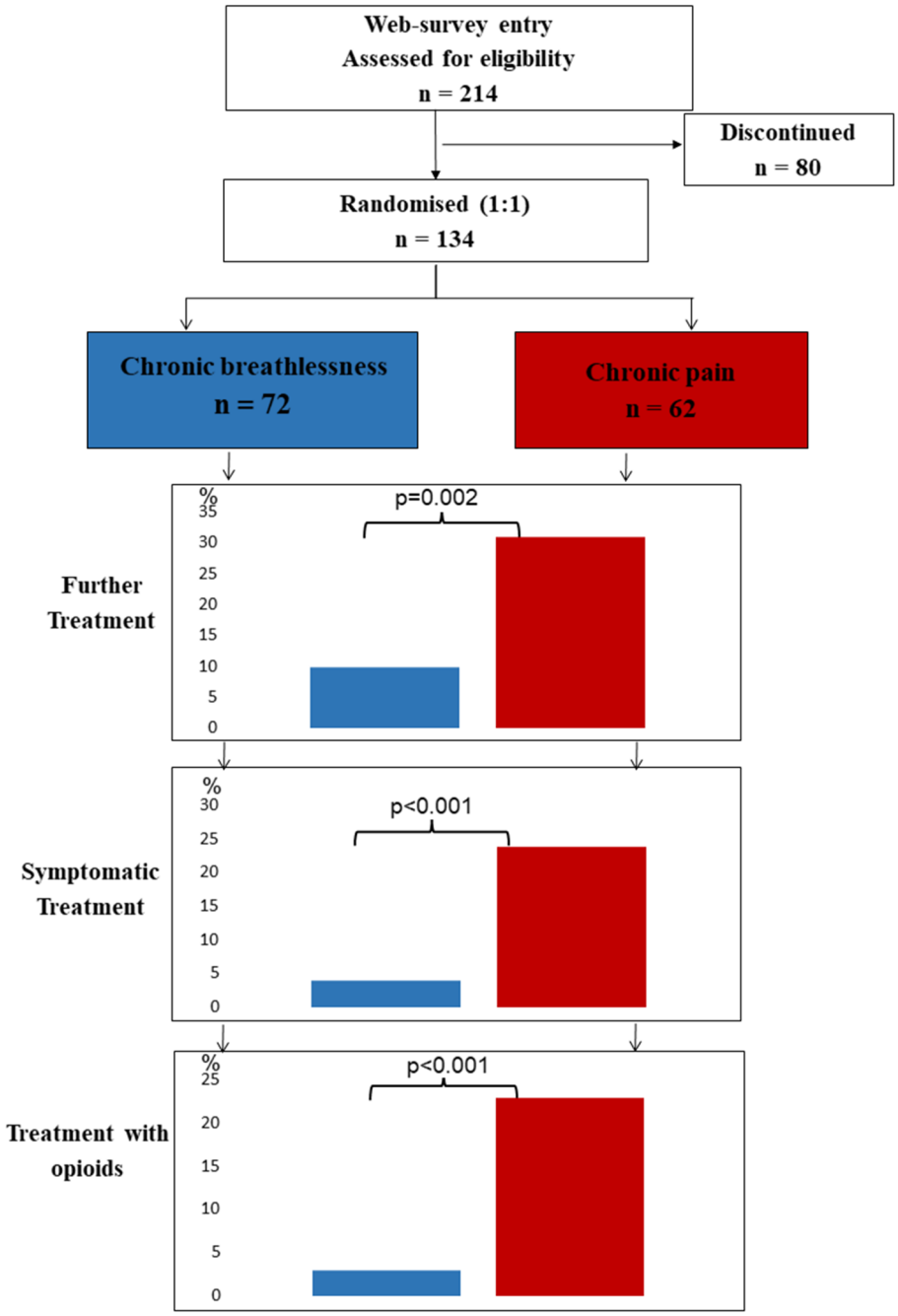


Figure 8. Study design and main findings.

Table 9. Management of a patient with optimally treated COPD and either chronic breathlessness or chronic pain.

	Breathlessness n=72 (%)	Pain n=62 (%)	p-value χ2-test
Further diagnostics	50 (70)	36 (58)	0.17
Active surveillance with a revisit	14 (19)	6 (10)	0.1
Optimal treatment, further contact as needed	1 (1)	1 (1)	0.9
Further treatment	7 (10)	19 (31)	0.002
For COPD	4 (5)	1 (2)	0.23
Symptomatic treatment	3 (4)	15 (24)	<0.001
Opioids	2 (3)	14 (23)	<0.001
Other treatment	0	3 (5)	0.06

Participants were randomized to a hypothetical case scenario of a patient with optimally treated COPD with, in a randomized fashion, either severe chronic breathlessness or chronic pain.

Findings were similar when adjusting for physician seniority and current working specialty: physicians were less likely to recognize the need for further treatment (OR 0.23; 95% CI, 0.08 – 0.64), less likely to offer symptomatic treatment for chronic breathlessness (OR 0.11; 95% CI, 0.03 – 0.43), and less likely to offer treatment with opioids (OR 0.11; 95% CI, 0.02 – 0.51) for COPD than for cancer.

Main reasons for not treating with opioids were fear of increased risk of adverse events such as confusion (39%), falls (35%), and addiction (34%); insufficient knowledge about indication for, and dosage of, opioids (32%); lack of detailed treatment guidelines (28%); and that opioids were considered relevant only in an end-of-life setting (20%). Reasons for not treating with opioids differed markedly for breathlessness compared to pain: insufficient knowledge of use and dosage of opioids (51% vs 4%; p <0.001), lack of optimal treatment guidelines (36% vs 17%; p=0.024), and opioids considered relevant only in an end-of-life setting (31% vs 4%; p <0.001). However, the risk of serious adverse events was perceived as similar in the symptom groups (Figure 9; Table 10).

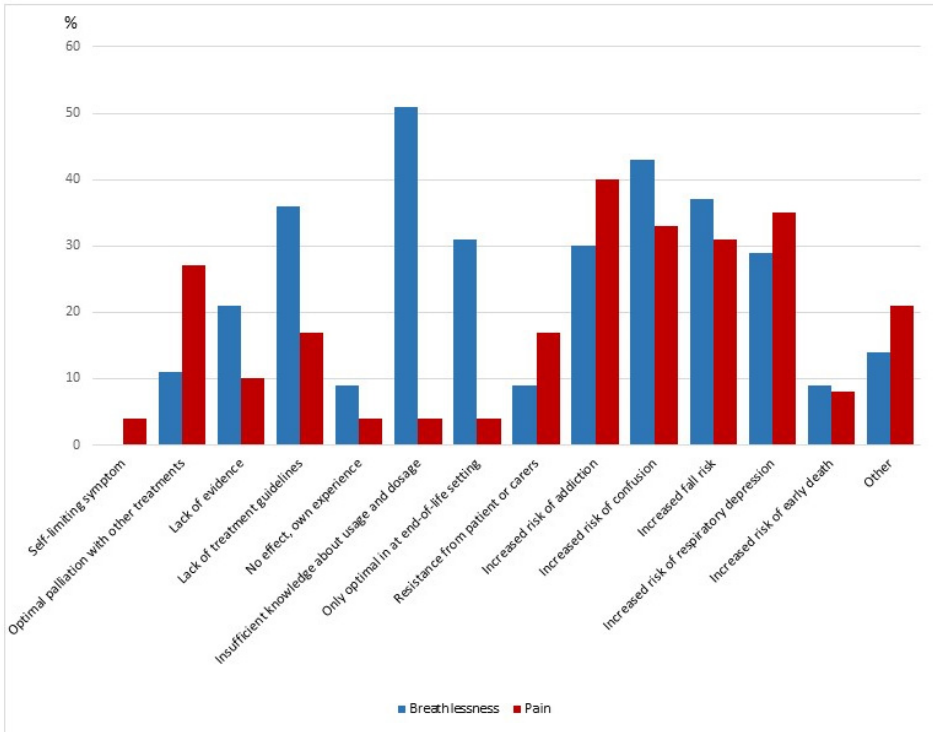


Figure 9. Reasons for not offering opioid treatment to relieve chronic breathlessness (n=70) vs. chronic pain (n=48).

Nearly all (n=129; 96%) physicians considered that the patient suffered from chronic breathlessness, defined as significant breathlessness despite optimal management for underlying treatable etiologies. Fewer physicians prescribed opioids in their clinical practice for chronic breathlessness than for chronic pain (18% vs 31%; p <0.001), and the number of physicians stating that they never prescribed opioids for breathlessness was significantly greater than those who never prescribed opioids for pain in patients with severe COPD (47% vs 17%; p <0.001; Table 11).

Table 10. Reasons for not offering opioid treatment to relieve chronic breathlessness vs chronic pain.

N (%)	All n=118	Opioid for breathlessness n=70 (%)	Opioid for pain n=48 (%)	p-value χ2-test
Self-limiting symptom	2 (2)	0	2 (4)	0.09
Optimal palliation is achieved with other treatments	21 (18)	8 (11)	13 (27)	0.024
Insufficient evidence for beneficial effect	20 (17)	15 (21)	5 (10)	0.12
Lack of treatment guidelines	33 (28)	25 (36)	8 (17)	0.03
No effect, own experience	8 (7)	6 (9)	2 (4)	0.35
Insufficient knowledge about usage and dosage	38 (32)	36 (51)	2 (4)	<0.001
Only relevant in an end-of-life setting	24 (20)	22 (31)	2 (4)	<0.001
Resistance from patient or carers	14 (12)	6 (9)	8 (17)	0.18
Increased risk of addiction	40 (34)	21 (30)	19 (40)	0.28
Increased risk of confusion	46 (39)	30 (43)	16 (33)	0.30
Increased fall risk	41 (35)	26 (37)	15 (31)	0.51
Increased risk of respiratory depression	37 (31)	20 (29)	17 (35)	0.43
Increased risk of early death	10 (9)	6 (9)	4 (8)	0.96
Other	20 (17)	10 (14)	10 (21)	0.35

Analyzed in physicians who did not offer treatment with opioids (n=118/134).

Table 11. Prescription of opioids by physicians in routine clinical practice.

How often do you prescribe opioids to treat breathlessness in severe COPD? vs How often do you prescribe opioids to treat pain in severe COPD?			
N (%)	Breathlessness	Pain	p-value χ2-test
Never	63 (47)	23 (17)	<0.001
Very rarely (occasionally/year)	47 (35)	69 (52)	<0.001
Ocassionally (few times/month)	18 (13)	31 (23)	<0.001
More often than ocassionally	6 (5)	11 (8)	<0.001

Physicians were asked about their prescription of opioids in clinical practice for treatment of breathlessness and for treatment of pain (non-randomized question).

Discussion

Main findings

Study I

Study I reported that COPD patients suffered higher levels of breathlessness and anxiety but less pain and nausea than did cancer patients during the final week of life [200]. Breathlessness was three times as common as pain before death in COPD. Poor symptom control remains a significant problem in the EOL setting. Prescription of as-needed medications for all symptoms was significantly lower in COPD patients than in those with cancer. Few previous studies have included the final few days of life, and most are out-dated or involved small cohorts [204, 205]. This study expanded previous findings with data on prescription of palliative medications during the last week of life, specifically in advanced COPD.

COPD patients were found to have limited access to specialized palliative care services and to receive less EOL care than patients with cancer, consistent with previous reports [204, 206]. The unpredictable course of COPD disease and the difficulty of predicting survival are commonly identified barriers to timely referral to specialized palliative care services [207].

Study II

This study found that opioids were commonly prescribed to oxygen-dependent COPD patients, with 46% of patients dispensed at least one prescription [201]. However, opioids were rarely used to treat breathlessness, as we found that the vast majority of the stated indications were pain (97%) and only 2% for breathlessness with a slight increase at the end of life.

The finding that opioids are rarely prescribed for breathlessness in COPD is consistent with previous studies [181, 208]. Physicians' fear of possible serious adverse events including respiratory depression, along with a lack of related knowledge and experience, have been commonly reported reasons for under prescribing of opioids [181, 182]. However, evidence to date supports the safety of low-dose opioids, with no reported associated increase in hospital admissions or mortality [169, 178, 180, 209]. A recent systematic review and meta-analysis found

no evidence of significant or clinically relevant adverse respiratory effects, but quality of the reviewed studies was a major limitation [185].

Study III

In Study III, a meta-analysis of available RCTs showed supplemental oxygen therapy to have a modest effect on breathlessness during exercise in COPD with no or mild hypoxemia [202]. Most evidence pertained to acute effects of oxygen therapy given during exercise testing in a laboratory setting. Evidence is less consistent and of low quality for effects of supplemental oxygen therapy on breathlessness during daily activities. The analysis of HRQOL showed no clear effect of supplemental oxygen therapy compared to air on quality of life.

The findings of this study were consistent with a Cochrane meta-analysis of research into the effects of ambulatory oxygen therapy by Ameer *et al.* (four studies; 331 participants), in which patients receiving oxygen therapy experienced a small reduction in breathlessness, inconsistent effect on HRQOL, and no clear impact on exercise capacity [163]. Recently, the Long-Term Oxygen Therapy Trial (n=738), reported no benefit on survival or time to first hospitalization and no effect on HRQOL in COPD patients with moderate hypoxemia at rest or during exertion [210].

An important finding was that supplemental oxygen therapy improved breathlessness measured only at iso-time, not at the end of exercise. The maximum symptom level measured at the end of an exercise test has limited value in quantifying the severity of breathlessness or the response to therapy; studies have shown that people with and without disease terminate exercise at similar levels of breathlessness [128]. A recent study of oral morphine reported significant reduction in exertional breathlessness at iso-time and increased exercise endurance in COPD with chronic breathlessness [169]. Together, these findings highlight the need to measure breathlessness at a standardized level of exertion in future studies, for example, at iso-time using comparable workloads in mechanistic studies and interventional trials [211].

Study IV

Study IV revealed that the physicians were less likely to identify chronic breathlessness as requiring treatment for symptom relief and also less likely to offer opioid treatment for chronic breathlessness than for chronic pain in a case study of a patient with COPD [203]. The findings are in agreement with previous clinical studies reporting that, although breathlessness is the dominant and most distressing symptom in patients with COPD, there is discrepancy between patients and their physicians in the perception of the symptom and its severity [95]. Reasons for under-recognition of the impact of breathlessness might be that breathlessness is so common in severe respiratory disease that it might simply be considered by

physicians, patients, and caregivers as an inevitable aspect of the patient's life. Other potential reasons may be that breathlessness is rarely systematically assessed or followed-up in clinical practice despite recommendations [96], and therapeutic nihilism may play a part. The present findings expand previous qualitative work [182, 208, 212] and non-randomized quantitative studies [181]. Due to randomization and the adjusted analysis, the differences in symptom recognition and management in this trial were independent of the physician´s practice specialty, level of seniority, and work experience.

Strengths and limitations

Study I

Sweden has a long tradition of national registries and register-based research. The Swedevox register was established in 1987 and has a population-based coverage of ~85% of patients beginning LTOT nationwide [160]. The SRPC register collects data on EOL care, and had coverage of 87% of all cancer deaths in Sweden in 2013 [188]. Strengths of the study include its national design with real-world data from the included registries. The study included a large cohort of both men and women with severe oxygen-dependent COPD and data of symptom prevalence during the final week of life. These features likely enhance the generalizability of our findings.

Limitations of the study include that data of palliative care in SRPC were, by design, collected retrospectively through an EOL questionnaire. The questionnaire is completed by staff and could be affected by recall or reporting bias. The difficulties of establishing a prognosis in advanced COPD makes prospective data collection near death problematic among severely ill patients. Staff proxy assessments of symptoms in patients with advanced disease have been reported to be a valid alternative to patient self-report, primarily in patients with cancer. The validity of proxy reports in COPD has not been established. In addition, data of treatment included prescriptions for as-needed medications, and it is not possible to say if or when the medications were administered and whether the symptoms responded to treatment or changed over time for other reasons. The cancer group was large and included various diagnoses, which could be a limitation. A sub-analysis comparing EOL care of COPD patients to those with lung cancer showed similar findings. Although patients with lung cancer had high levels of most of the other symptoms, breathlessness remained more common in COPD.

Study II

Strengths of the study include its national population-based design. Complete longitudinal data on all dispensed outpatient opioid prescriptions were available from the Prescribed Drug Register, and data of COPD patients with LTOT nationwide was obtained from Swedevox. National register data enabled complete follow-up in these frail patients with advanced disease. The use of a randomized prescription sample enabled analysis of the free-text indications, and the timing of prescription was analyzed in relation to LTOT and death.

A limitation was that a high proportion of prescriptions lacked a stated indication. This reflects clinical reality and is an important finding in its own right, as it identifies an area for potential improvement in clinical practice. In Sweden, the opioid indication is not externally reviewed and does not affect the price or the patient ability to access an opioid prescription; thus, a lack of stated indication would probably not to lead to bias. Prescription data did not include opioids administered in hospital, but this is unlikely to substantially change the data of treatment indications. It would seem unlikely to prescribe opioids for breathlessness during hospitalization but not continue with renewed prescriptions in the outpatient setting. Another possible limitation is that the study included data from 2005 through 2009, because data was available only from that time period. However, evidence that supported the use of opioids for the relief of breathlessness was available from a Cochrane meta-analysis published in 2002 and an adequately powered trial published in 2003 [174, 175]. Patient-reported data including breathlessness and quality of life scores were not available to further characterize patients in this study.

Study III

Strengths of the study are that the systematic review and meta-analysis were conducted according to the framework and guidelines of the Cochrane Collaboration, with attention to the quality of included studies. Rigorous peer review of study protocol and the systematic review was conducted within the collaboration. The findings of the principle analysis of breathlessness were consistent with a previous review [162] and provided more precise estimates, as additional studies were included. Several sub-analyses and novel analysis of HRQOL were also carried out.

Limitations of this systematic review primarily pertain to the methodological heterogeneity among studies. Although we excluded studies of LTOT, the included population had a wide range of baseline oxygen saturation or PaO_2. This variation could have affected results if a relationship exists between oxygen saturation and effects of oxygen therapy on breathlessness. A subgroup analysis was conducted using baseline PaO_2 ($\geq$9.3 kPa) and resulted in consistent findings. In addition, baseline breathlessness and exercise capacity were often insufficiently reported.

There were some limitations regarding the studies; for example, participants with varying degrees of exercise capacity were included, and it remains unclear if the oxygen equipment was of optimal quality and the dose adequate, and whether patients adhered to the prescribed oxygen therapy. These factors might affect efficacy of supplemental oxygen therapy in daily activities. Adverse events were insufficiently assessed and/or reported in the studies.

We explored potential bias due to methodological limitations with a sensitivity analysis excluding studies with high risk for bias, which yielded findings consistent with the primary analysis. A possible limitation of this review is that many studies did not report data on participants who withdrew from the study, which might have introduced selection bias.

Obtained effects of supplemental oxygen therapy on breathlessness were driven in part by five outlier findings of studies with small sample sizes and low levels of precision. This asymmetry in the funnel plot might indicate the presence of publication bias. When we excluded the outliers, the obtained effect of supplemental oxygen therapy was slightly reduced (SMD -0.24, 95% CI -0.34 – -0.15). Avoidance of publication bias in meta-analysis is important. Although the funnel plot indicated potential publication bias, we did not downgrade the quality of the evidence, as a sensitivity analysis excluding outlying studies yielded similar findings.

Study IV

Major strengths of the study include its randomized, double-blind parallel-group design with characteristics well balanced between the groups and analyses adjusted for potential confounders. Participants were unaware of the randomization and study aims. By design, participants could not review or change previous answers, and all questions had to be answered before proceeding to the next question. The design facilitated conclusions about the clinical response to two dominant chronic symptoms in severe disease.

Physicians across different settings were included; half of the participants worked in a hospital setting and half in primary care. Besides surveying intended treatment plans in a randomized case scenario, actual opioid prescription patterns in clinical practice were surveyed, which were consistent with the hypothetical case and support the validity of the present findings.

A potential limitation is that the trial did not reach the intended sample size. However, the actual between-group differences were greater than expected, which resulted in obtaining the target statistical power for the primary analysis. It is possible that the difference observed may have been due to random variation, but this seems unlikely, since the difference was consistent across outcomes, and the sample size was near target size.

Management decisions in clinical practice may differ from responses to a hypothetical case scenario. However, the scenario represented a patient category that is frequently encountered in clinical practice, and participants were carefully instructed to answer in accordance with their usual management. Moreover, the reluctance to treat with opioids for breathlessness was consistent with the participating physicians' self-reported practice in this survey, with fewer physicians prescribing opioids for chronic breathlessness than for chronic pain. This finding was in accordance with previous observational studies [181, 182, 208, 213] and, together with the blinded randomized design, supports the validity of the main findings of the study.

Significance

Study I

The COPD patients were found to receive less EOL care than patients with cancer, consistent with previous reports [206, 214], which suggests an unequal distribution of specialized palliative resources at the EOL, depending on underlying disease, and points to a potential area for improvement. There is a high prevalence of breathlessness among patients with advanced COPD in the EOL setting. For clinicians, the findings of the study highlight the need for adequate EOL care among patients with advanced COPD. This includes optimal symptom management and increased access to specialized palliative care services [146].

Study I provides information of current circumstances and health care needs of patients with severe COPD and cancer in their final days in Sweden, and is relevant to similar settings worldwide. The analyses of symptoms and provision of specialized palliative care in severe non-malignant respiratory disease is imperative, as supportive and symptomatic treatment may be underused. New models of care that integrate early palliative care within respiratory medicine have demonstrated improved patient outcomes [146, 215, 216]. Over the coming decades, interdisciplinary collaboration between respiratory and palliative medicine is likely to increase.

Study II

The finding of Study II that opioids are rarely prescribed for relief of breathlessness in advanced COPD suggest that there is a need for practical guidelines for implementing available evidence-based treatment of breathlessness in clinical practice, including clear standards for when to initiate opioid treatment, initial dose, dose titration, and clinical review for efficacy.

Given the growing body of evidence for efficacy and safety, low-dose opioids can be prescribed with greater confidence for the relief of refractory breathlessness in advanced COPD [217]. In the COPD population, sustained-release morphine should be initiated at a low regular dose and titrated upward over days and weeks, balancing beneficial and adverse effects [178]. Adequate follow-up to assess patient clinical condition and symptom relief, including proper prophylaxis and treatment of expected side-effects such as constipation, should be planned. Many questions regarding optimal treatment with opioids remain unanswered, and large-scale longitudinal studies are needed to evaluate their net benefit in clinical practice. There is a need for larger studies designed to detect adverse respiratory effects. The results of the ongoing Morphine for Dyspnea in COPD study, which focuses primarily on adverse respiratory effects, would add valuable information to this field [218].

An indication was not provided for many prescriptions recorded in this study, and a potential implication is that clear information regarding the indication and purpose of the medication is imperative and should be included for all prescriptions. This is essential to ensure the safety of therapy, patience compliance, and symptom control, especially in sick elderly patients and when informal caretakers are involved.

Study III

This study found no evidence to support the use of supplemental oxygen therapy for relief of breathlessness in daily activities in COPD patients with no or mild hypoxemia. In contrast, supplemental oxygen therapy was demonstrated to provide relief of breathlessness in a laboratory setting. Findings of this review were consistent with British Thoracic Society guidelines published in 2015: ambulatory oxygen therapy should be offered to patients for use during exercise in a pulmonary rehabilitation program and "should not be routinely offered to patients who are not eligible for LTOT" [59]. Although our review confirmed that supplemental oxygen therapy can decrease exertional breathlessness in the laboratory setting, studies should focus on effects of domiciliary and ambulatory oxygen in clinical and daily life settings.

The findings of Study III that supplemental oxygen therapy affected breathlessness measured only at iso-time suggest that breathlessness should be measured at a standardized level of exertion in future studies; for example, at iso-time with comparable workloads in mechanistic studies and intervention trials [211]. This observation is consistent with that reported for other interventions, such as for morphine by Abdallah *et al.* [169]. The issue of non-standardized exertion also applies to questionnaires (uni- and multi-dimensional) assessing breathlessness during daily activity. The frequency, intensity, and distress of breathlessness can be modified by the patient through adapting the level of physical activity. Self-reported walking distance is a subjective measure that does not correlate with known

measures of exercise capacity. Breathlessness is a multidimensional symptom that may be influenced by psychosocial factors; thus, appropriate state and trait measures should be collected.

Studies quantifying adverse events, patient burden, and potential risks associated with supplemental oxygen therapy are required to determine the net clinical benefit of palliative oxygen. In this review, adverse events were insufficiently assessed and/or reported. The first population-based longitudinal study of the risk of burn injury during supplemental oxygen therapy was recently published [167].

Evaluation of the potential benefit of supplemental oxygen should involve the patient's level of physical capacity and activity, along with the benefits of oxygen for breathlessness and on physical capacity in a standardized test when compared with air [59]. Patients who perceive decreased breathlessness when receiving supplemental oxygen most often experience this effect within two to three days [219]. Therefore, palliative oxygen therapy should be evaluated after a few days and withdrawn if patients do not perceive benefit. Patient quality of life factors such as convenience and adverse consequences should be considered in the decision of whether to prescribe supplemental oxygen for patients who are already burdened by illness.

Study IV

Physicians were less likely to identify breathlessness, compared to pain, as a candidate for symptomatic treatment in our hypothetical case study. As healthcare professionals we might wrongly believe that nothing can be done to relieve breathlessness, especially if we do not have an understanding of the widespread impact of chronic breathlessness on quality of life or knowledge of recommended evidence-based interventions. Another potential impediment to expanded care could be that breathlessness is rarely systematically assessed or followed-up in clinical practice, despite recommendations [96].

For clinicians, this study highlights the need to more actively identify symptoms and, especially for chronic breathlessness, to systematically evaluate their impact in daily practice and to actively consider symptomatic treatment. Clinicians may be concerned about the time pressures restricting holistic assessment and poor access to non-pharmacological interventions, especially psychological interventions.

Future aspects

Assessment and treatment of breathlessness in advanced COPD can be improved in several important areas. Although validated scales, both unidimensional and multidimensional, are available for identification of intensity, quality, and functional impact of breathlessness, most are impractical in routine clinical care. There is a need for a standard measurement tool that is informative and feasible in daily clinical practice.

Breathlessness should be assessed at a standardized level of exertion both in clinical practice and in future research. The failure to account for the level of exertion and factors provoking symptoms can lead to false positive effects in trials in which a decrease in reported breathlessness may reflect decreased activity or avoidance of situations that provoke symptoms rather than symptom improvement; or to false-negative results (lack of change in measured breathlessness despite actual symptom improvement), as the patient may be able to achieve higher levels of exertion before the same symptom threshold of breathlessness is reached [211]. This could, at least partly, explain the discordance between treatments such as supplemental oxygen therapy and opioids, in which an effect on breathlessness was seen at iso-time at a standardized exertion level but not when measured at the end of the exercise trial or a questionnaire pertaining to daily activity [169, 202]. Emerging field tests for measuring exertional breathlessness, including a 3-min step test and 3-min constant-rate shuttle walk test, have shown responsiveness to changes in breathlessness resulting from bronchodilation in COPD [220-222]. Validated multidimensional questionnaires such as the MDP could be used during standardized exertion.

Although sustained-release morphine has been recently registered for treatment of chronic breathlessness in Australia, unanswered questions remain. Future longer-term studies are needed to evaluate the relative efficacy of opioids, to determine effects on daily activity and quality of life, to identify which patients respond and benefit from opioids, to establish dose titration, and to assess the safety profile of opioids. There is also a need for more evidence regarding non-opioid pharmacologic treatments such as nebulized furosemide, which has been shown to relieve experimental [223-225] and clinical breathlessness [226, 227]. A Cochrane review and meta-analysis on the efficacy of inhaled furosemide for relief of breathlessness is planned by our research group.

Although there are grounds for optimism as research in this important field of chronic breathlessness continues to expand, it is important that high quality studies are designed using standardized exercise protocols in order to not overlook potential beneficial treatments or overestimate study results of chronic breathlessness.

Conclusions

Study I

COPD patients suffer from a high burden of symptoms, especially breathlessness, at the end of life. In Sweden, COPD patients have limited access to specialized care services and receive less end of life care than patients with cancer.

Study II

Opioids are commonly prescribed to patients with oxygen-dependent COPD, predominantly for pain. Pain was the indication in 97% and breathlessness in only 2% of the opioid prescriptions in COPD.

Study III

Supplemental oxygen therapy modestly reduces breathlessness during exercise in COPD with no or mild hypoxemia. Oxygen therapy for breathlessness demonstrates no clear benefits during daily activities or on quality of life.

Study IV

Patients with chronic breathlessness are less likely to be identified by physicians as candidates for symptomatic treatment and also less likely to be offered treatment with opioids compared to patients exhibiting chronic pain.

Acknowledgements

My supervisor, ***Magnus Ekström*** - What a journey this has been? Thank you for making this research journey not only full of new insights on how to conduct research but also a fun experience! You have with patience guided me through this fascinating world of science and research and generously invested so much time and effort in me. Thank you for the 100,000 emails we have exchanged over the years! Your enthusiasm is mesmerizing, inspiring, and has no limits! I hope I can in future become a self-sufficient researcher and a mentor like you!

My co-supervisor, ***Kjell Torén***, for sharing your expertise in epidemiology and your support. I look forward to future studies with you!

Anna-Bornefalk Hermansson, you really are a superb statistician! Thank you for your invaluable help with statistical analyses, especially with Paper III.

I would like to express my gratitude to all my co-authors, both from Sweden and around the world, for great team work and insightful comments on the papers. A special thanks to Professor ***David Currow*** for your constructive feedback on the papers.

I am grateful to ***Johan Svahn***, current head of our department, for giving me a residency within respiratory medicine and for being so understanding and flexible.

Jonas Einarsson, my clinical supervisor and outstanding physician, thank you for your encouragement and believing in me.

Bengt Midgren, thank you for sharing with me your immense knowledge of respiratory medicine and proofreading the thesis.

Thank you to all of my colleagues for being such fantastic colleagues and for your endless support and clinical mentoring during my residency. I am eternally thankful for everything I have learned from you and need to learn in future. It is you all that make the Respiratory Medicine department the greatest group to be part of and I am so happy to be one of you.

Special thanks for my fellow “ST-läkare” for being awesome!

I am grateful for financial support through the ST-ALF Skåne, the Swedish Heart-Lung Foundation, the Swedish Society of Medicine, and the Research Council of Blekinge that made this PhD possible.

A big thanks to all the people who collected the research data in the registries and cared for the patients throughout the years, without whom this thesis would not have been possible.

Mom and Dad, from the bottom of my heart, I love you forever! Thank you for your unconditional love and all the sacrifices you have done for your children. Dad – I appreciate your kind and supportive words of always telling me to believe in myself and pursue knowledge and move forward! Mom – thank you for your warmth and being the best and sweetest mom in the world!

My fantastic brother, ***Mahmood***, and sister ***Mahboobah***, thank you for introducing me to research and for your incredible support and encouragement the whole time! Never would I have thought that research would be fun and I would become a researcher!

My lovely sister, ***Bahar*** – thank you for all the laughs and the wonderful conversations we have had these recent years! I just need to ask if you would like to be my personal shrink? I might need one after this thesis!

References

1. *Global strategy for the diagnosis, management and treatment of chronic obstructive lung disease (2019 Report).* Global initiative for chronic obstructive lung disease (GOLD). Available from https://goldcopd.org/.
2. Rennard, S., et al., *Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey.* Eur Respir J, 2002. **20**(4): p. 799-805.
3. Celli, B.R., et al., *Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper.* European Respiratory Journal, 2004. **23**(6): p. 932-946.
4. Woodruff, P.G., et al., *Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function.* N Engl J Med, 2016. **374**(19): p. 1811-21.
5. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-2128.
6. Adeloye, D., et al., *Global and regional estimates of COPD prevalence: Systematic review and meta-analysis.* J Glob Health, 2015. **5**(2): p. 020415.
7. Toren, K., et al., *Vital capacity and COPD: the Swedish CArdioPulmonary bioImage Study (SCAPIS).* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 927-33.
8. Backman, H., et al., *Decreased prevalence of moderate to severe COPD over 15 years in northern Sweden.* Respir Med, 2016. **114**: p. 103-10.
9. Mathers, C.D. and D. Loncar, *Projections of global mortality and burden of disease from 2002 to 2030.* Plos Medicine, 2006. **3**(11).
10. Lisspers, K., et al., *Economic burden of COPD in a Swedish cohort: the ARCTIC study.* Int J Chron Obstruct Pulmon Dis, 2018. **13**: p. 275-285.
11. Jansson, S.A., et al., *Hospitalization Due to Co-Morbid Conditions is the Main Cost Driver Among Subjects With COPD-A Report From the Population-Based OLIN COPD Study.* COPD, 2015. **12**(4): p. 381-9.
12. Forey, B.A., A.J. Thornton, and P.N. Lee, *Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema.* BMC Pulmonary Medicine, 2011. **11**: p. 36.
13. Eisner, M.D., et al., *An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease.* American Journal of Respiratory and Critical Care Medicine, 2010. **182**(5): p. 693-718.
14. Fletscher, C., et al., *The natural history of chronic bronchitis and emphysema*. 1976, Oxford: Oxford University Press.

15. Lange, P., et al., *Effects of smoking and changes in smoking habits on the decline of FEV1.* Eur Respir J, 1989. **2**(9): p. 811-6.
16. Xu, X., et al., *Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences.* Eur Respir J, 1994. **7**(6): p. 1056-61.
17. Lange, P., et al., *Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease.* N Engl J Med, 2015. **373**(2): p. 111-22.
18. Lindberg, A., et al., *Seven-year cumulative incidence of COPD in an age-stratified general population sample.* Chest, 2006. **129**(4): p. 879-85.
19. Stoller, J.K. and L.S. Aboussouan, *Alpha1-antitrypsin deficiency.* Lancet, 2005. **365**(9478): p. 2225-36.
20. Wilk, J.B., et al., *Framingham Heart Study genome-wide association: results for pulmonary function measures.* BMC Medical Genetics, 2007. **8 Suppl 1**: p. S8.
21. Repapi, E., et al., *Genome-wide association study identifies five loci associated with lung function.* Nat Genet, 2010. **42**(1): p. 36-44.
22. Bakke, P.S., et al., *Candidate genes for COPD in two large data sets.* European Respiratory Journal, 2011. **37**(2): p. 255-263.
23. Martinez, F.J., et al., *Sex differences in severe pulmonary emphysema.* American Journal of Respiratory and Critical Care Medicine, 2007. **176**(3): p. 243-52.
24. Lange, P., et al., *A 15-year follow-up study of ventilatory function in adults with asthma.* The New England journal of medicine, 1998. **339**(17): p. 1194-200.
25. Lopez, A.D., et al., *Global burden of disease and risk factors*. 2006, Washington: The World Bank.
26. Salvi, S.S. and P.J. Barnes, *Chronic obstructive pulmonary disease in non-smokers.* Lancet, 2009. **374**(9691): p. 733-43.
27. Hogg, J.C. and W. Timens, *The Pathology of Chronic Obstructive Pulmonary Disease.* Annual Review of Pathology: Mechanisms of Disease, 2009. **4**(1): p. 435-459.
28. Hogg, J.C., P.T. Macklem, and W.M. Thurlbeck, *Site and nature of airway obstruction in chronic obstructive lung disease.* N Engl J Med, 1968. **278**(25): p. 1355-60.
29. Yanai, M., et al., *Site of airway obstruction in pulmonary disease: direct measurement of intrabronchial pressure.* J Appl Physiol (1985), 1992. **72**(3): p. 1016-23.
30. O'Donnell, D.E., *Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease.* Proc Am Thorac Soc, 2006. **3**(2): p. 180-4.
31. Hogg, J.C., et al., *The nature of small-airway obstruction in chronic obstructive pulmonary disease.* N Engl J Med, 2004. **350**(26): p. 2645-53.
32. Higham, A., et al., *The pathology of small airways disease in COPD: historical aspects and future directions.* Respir Res, 2019. **20**(1): p. 49.
33. Stockley, R.A., *Neutrophils and protease/antiprotease imbalance.* Am J Respir Crit Care Med, 1999. **160**(5 Pt 2): p. S49-52.
34. Kulkarni, T., et al., *Matrix Remodeling in Pulmonary Fibrosis and Emphysema.* Am J Respir Cell Mol Biol, 2016. **54**(6): p. 751-60.
35. McDonough, J.E., et al., *Small-airway obstruction and emphysema in chronic obstructive pulmonary disease.* N Engl J Med, 2011. **365**(17): p. 1567-75.

36. Koo, H.K., et al., *Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study.* Lancet Respir Med, 2018. **6**(8): p. 591-602.
37. Churg, A., et al., *Cigarette smoke drives small airway remodeling by induction of growth factors in the airway wall.* Am J Respir Crit Care Med, 2006. **174**(12): p. 1327-34.
38. Sakao, S., N.F. Voelkel, and K. Tatsumi, *The vascular bed in COPD: pulmonary hypertension and pulmonary vascular alterations.* Eur Respir Rev, 2014. **23**(133): p. 350-5.
39. Chaouat, A., R. Naeije, and E. Weitzenblum, *Pulmonary hypertension in COPD.* The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology, 2008. **32**(5): p. 1371-85.
40. Kim, V., T.J. Rogers, and G.J. Criner, *New concepts in the pathobiology of chronic obstructive pulmonary disease.* Proc Am Thorac Soc, 2008. **5**(4): p. 478-85.
41. Chung, K.F. and I.M. Adcock, *Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction.* Eur Respir J, 2008. **31**(6): p. 1334-56.
42. Barnes, P.J. and B.R. Celli, *Systemic manifestations and comorbidities of COPD.* European Respiratory Journal, 2009. **33**(5): p. 1165-85.
43. Nussbaumer-Ochsner, Y. and K.F. Rabe, *Systemic Manifestations of COPD.* Chest, 2011. **139**(1): p. 165-173.
44. Wedzicha, J.A. and T.A. Seemungal, *COPD exacerbations: defining their cause and prevention.* Lancet, 2007. **370**(9589): p. 786-96.
45. Barbera, J.A., et al., *Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease.* Eur Respir J, 1997. **10**(6): p. 1285-91.
46. Parker, C.M., et al., *Physiological changes during symptom recovery from moderate exacerbations of COPD.* Eur Respir J, 2005. **26**(3): p. 420-8.
47. Force, U.S.P.S.T., et al., *Screening for Chronic Obstructive Pulmonary Disease: US Preventive Services Task Force Recommendation Statement.* JAMA, 2016. **315**(13): p. 1372-7.
48. Hardie, J.A., et al., *Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers.* European Respiratory Journal, 2002. **20**(5): p. 1117-1122.
49. Kohler, D., et al., *Usefulness of GOLD classification of COPD severity.* Thorax, 2003. **58**(9): p. 825.
50. Hansen, J.E., X.G. Sun, and K. Wasserman, *Spirometric criteria for airway obstruction: Use percentage of FEV1/FVC ratio below the fifth percentile, not < 70%.* Chest, 2007. **131**(2): p. 349-55.
51. Mannino, D.M., A. Sonia Buist, and W.M. Vollmer, *Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function?* Thorax, 2007. **62**(3): p. 237-41.
52. Rothnie, K.J., et al., *Natural History of Chronic Obstructive Pulmonary Disease Exacerbations in a General Practice-based Population with Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2018. **198**(4): p. 464-471.

53. Bestall, J.C., et al., *Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.* Thorax, 1999. **54**(7): p. 581-6.
54. Gupta, N., et al., *The COPD assessment test: a systematic review.* Eur Respir J, 2014. **44**(4): p. 873-84.
55. Riley, C.M. and F.C. Sciurba, *Diagnosis and Outpatient Management of Chronic Obstructive Pulmonary Disease: A Review.* JAMA, 2019. **321**(8): p. 786-797.
56. Agusti, A., et al., *Inhaled corticosteroids in COPD: friend or foe?* Eur Respir J, 2018. **52**(6).
57. Cazzola, M., et al., *Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis.* Eur Respir J, 2018. **52**(6).
58. McCarthy, B., et al., *Pulmonary rehabilitation for chronic obstructive pulmonary disease.* Cochrane Database of Systematic Reviews, 2015(2).
59. Hardinge, M., et al., *British Thoracic Society guidelines for home oxygen use in adults.* Thorax, 2015. **70 Suppl 1**: p. i1-43.
60. *Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial.* Ann Intern Med, 1980. **93**(3): p. 391-8.
61. *Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema.* Lancet, 1981. **1**(8222): p. 681-6.
62. Mannino, D.M., et al., *Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD.* Eur Respir J, 2008. **32**(4): p. 962-9.
63. Murphy, P.B., et al., *Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial.* JAMA, 2017. **317**(21): p. 2177-2186.
64. Criner, G.J., et al., *A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE).* Am J Respir Crit Care Med, 2018. **198**(9): p. 1151-1164.
65. Fishman, A., et al., *A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema.* N Engl J Med, 2003. **348**(21): p. 2059-73.
66. Currow, D.C., et al., *Do the Trajectories of Dyspnea Differ in Prevalence and Intensity By Diagnosis at the End of Life? A Consecutive Cohort Study.* Journal of Pain and Symptom Management, 2010. **39**(4): p. 680-690.
67. Duenk, R.G., et al., *The view of pulmonologists on palliative care for patients with COPD: a survey study.* Int J Chron Obstruct Pulmon Dis, 2017. **12**: p. 299-311.
68. Vermylen, J.H., E. Szmuilowicz, and R. Kalhan, *Palliative care in COPD: an unmet area for quality improvement.* Int J Chron Obstruct Pulmon Dis, 2015. **10**: p. 1543-51.

69. Parshall, M.B., et al., *An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea.* Am J Respir Crit Care Med, 2012. **185**(4): p. 435-52.
70. Johnson, M.J., et al., *Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness.* Eur Respir J, 2017. **49**(5).
71. Lansing, R.W., R.H. Gracely, and R.B. Banzett, *The multiple dimensions of dyspnea: review and hypotheses.* Respir Physiol Neurobiol, 2009. **167**(1): p. 53-60.
72. Gift, A.G. and G. Narsavage, *Validity of the numeric rating scale as a measure of dyspnea.* Am J Crit Care, 1998. **7**(3): p. 200-4.
73. Bausewein, C., et al., *Measurement of breathlessness in advanced disease: a systematic review.* Respir Med, 2007. **101**(3): p. 399-410.
74. Ries, A.L., *Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale.* COPD, 2005. **2**(1): p. 105-10.
75. Banzett, R.B., et al., *Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research.* European Respiratory Journal, 2015. **45**(6): p. 1681-1691.
76. Meek, P.M., et al., *Reliability and validity of the multidimensional dyspnea profile.* Chest, 2012. **141**(6): p. 1546-53.
77. Yorke, J., et al., *Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12.* Thorax, 2010. **65**(1): p. 21-6.
78. Banzett, R.B., et al., *Air hunger from increased pco2 persists after complete neuromuscular block in humans.* Respiration Physiology, 1990. **81**(1): p. 1-18.
79. Meguro, M., et al., *Development and Validation of an Improved, COPD-Specific Version of the St. George Respiratory Questionnaire.* Chest, 2007. **132**(2): p. 456-63.
80. Wijkstra, P.J., et al., *Reliability and validity of the chronic respiratory questionnaire (CRQ).* Thorax, 1994. **49**(5): p. 465-7.
81. Simon, P.M., et al., *Distinguishable types of dyspnea in patients with shortness of breath.* Am Rev Respir Dis, 1990. **142**(5): p. 1009-14.
82. Elliott, M.W., et al., *The language of breathlessness. Use of verbal descriptors by patients with cardiopulmonary disease.* Am Rev Respir Dis, 1991. **144**(4): p. 826-32.
83. Nishino, T., *Dyspnoea: underlying mechanisms and treatment.* Br J Anaesth, 2011. **106**(4): p. 463-74.
84. Gronseth, R., et al., *Predictors of dyspnoea prevalence: results from the BOLD study.* Eur Respir J, 2014. **43**(6): p. 1610-20.
85. Currow, D.C., et al., *A community population survey of prevalence and severity of dyspnea in adults.* J Pain Symptom Manage, 2009. **38**(4): p. 533-45.
86. Muellerova, H., et al., *Prevalence and Burden of Breathlessness in Patients with Chronic Obstructive Pulmonary Disease Managed in Primary Care.* Plos One, 2014. **9**(1).

87. Currow, D.C., et al., *Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups.* Thorax, 2017. **72**(12): p. 1151-1153.
88. Nishimura, K., et al., *Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD.* Chest, 2002. **121**(5): p. 1434-1440.
89. Voll-Aanerud, M., et al., *Respiratory symptoms in adults are related to impaired quality of life, regardless of asthma and COPD: results from the European community respiratory health survey.* Health Qual Life Outcomes, 2010. **8**: p. 107.
90. Johnson, M.J., et al., *Breathlessness in Elderly Adults During the Last Year of Life Sufficient to Restrict Activity: Prevalence, Pattern, and Associated Factors.* J Am Geriatr Soc, 2016. **64**(1): p. 73-80.
91. Maurer, J., et al., *Anxiety and depression in COPD: current understanding, unanswered questions, and research needs.* Chest, 2008. **134**(4 Suppl): p. 43S-56S.
92. Waschki, B., et al., *Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2015. **192**(3): p. 295-306.
93. Ramon, M.A., et al., *The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model.* Eur Respir J, 2018. **52**(3).
94. Janssens, T., et al., *Dyspnea perception in COPD: association between anxiety, dyspnea-related fear, and dyspnea in a pulmonary rehabilitation program.* Chest, 2011. **140**(3): p. 618-625.
95. Miravitlles, M., et al., *Differences between physician and patient in the perception of symptoms and their severity in COPD.* Respir Med, 2013. **107**(12): p. 1977-85.
96. Mularski, R.A., et al., *A Review of Quality of Care Evaluation for the Palliation of Dyspnea.* American Journal of Respiratory and Critical Care Medicine, 2010. **181**(6): p. 534-538.
97. Currow, D.C., A.P. Abernethy, and D.N. Ko, *The active identification and management of chronic refractory breathlessness is a human right.* Thorax, 2014. **69**(4): p. 393-4.
98. Basoglu, M., *Effective management of breathlessness: a review of potential human rights issues.* Eur Respir J, 2017. **49**(5).
99. O'Donnell, D.E., *Breathlessness in patients with chronic airflow limitation. Mechanisms and management.* Chest, 1994. **106**(3): p. 904-12.
100. Laviolette, L. and P. Laveneziana, *Dyspnoea: a multidimensional and multidisciplinary approach.* Eur Respir J, 2014. **43**(6): p. 1750-62.
101. O'Donnell, D.E., et al., *Mechanisms of activity-related dyspnea in pulmonary diseases.* Respiratory Physiology & Neurobiology, 2009. **167**(1): p. 116-132.
102. Schwartzstein, R.M., et al., *Breathlessness induced by dissociation between ventilation and chemical drive.* Am Rev Respir Dis, 1989. **139**(5): p. 1231-7.

103. Manning, H.L., E.J. Molinary, and J.C. Leiter, *Effect of inspiratory flow rate on respiratory sensation and pattern of breathing.* Am J Respir Crit Care Med, 1995. **151**(3 Pt 1): p. 751-7.
104. Killian, K.J., et al., *Effect of increased lung volume on perception of breathlessness, effort, and tension.* J Appl Physiol Respir Environ Exerc Physiol, 1984. **57**(3): p. 686-91.
105. Lansing, R.W., et al., *The perception of respiratory work and effort can be independent of the perception of air hunger.* Am J Respir Crit Care Med, 2000. **162**(5): p. 1690-6.
106. Pattinson, K.T. and M.J. Johnson, *Neuroimaging of central breathlessness mechanisms.* Curr Opin Support Palliat Care, 2014. **8**(3): p. 225-33.
107. von Leupoldt, A., et al., *Dyspnea and pain share emotion-related brain network.* Neuroimage, 2009. **48**(1): p. 200-6.
108. Herigstad, M., et al., *Dyspnoea and the brain.* Respir Med, 2011. **105**(6): p. 809-17.
109. von Leupoldt, A. and B. Dahme, *Cortical substrates for the perception of dyspnea.* Chest, 2005. **128**(1): p. 345-354.
110. Davenport, P.W. and A. Vovk, *Cortical and subcortical central neural pathways in respiratory sensations.* Respir Physiol Neurobiol, 2009. **167**(1): p. 72-86.
111. Stoeckel, M.C., et al., *Brain Responses during the Anticipation of Dyspnea.* Neural Plast, 2016. **2016**: p. 6434987.
112. Evans, K.C., *Cortico-limbic circuitry and the airways: insights from functional neuroimaging of respiratory afferents and efferents.* Biol Psychol, 2010. **84**(1): p. 13-25.
113. von Leupoldt, A., et al., *The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala.* American Journal of Respiratory and Critical Care Medicine, 2008. **177**(9): p. 1026-1032.
114. Hayen, A., et al., *Opioid suppression of conditioned anticipatory brain responses to breathlessness.* Neuroimage, 2017. **150**: p. 383-394.
115. Faull, O.K., et al., *Chronic breathlessness: re-thinking the symptom.* Eur Respir J, 2018. **51**(1).
116. Van den Bergh, O., et al., *Symptoms and the body: Taking the inferential leap.* Neurosci Biobehav Rev, 2017. **74**(Pt A): p. 185-203.
117. Faull, O.K., A. Hayen, and K.T.S. Pattinson, *Breathlessness and the body: Neuroimaging clues for the inferential leap.* Cortex, 2017. **95**: p. 211-221.
118. Herigstad, M., et al., *Treating breathlessness via the brain: changes in brain activity over a course of pulmonary rehabilitation.* Eur Respir J, 2017. **50**(3).
119. Barrett, L.F. and W.K. Simmons, *Interoceptive predictions in the brain.* Nat Rev Neurosci, 2015. **16**(7): p. 419-29.
120. Faull, O.K., et al., *Conditioned respiratory threat in the subdivisions of the human periaqueductal gray.* Elife, 2016. **5**.
121. Borges-Santos, E., et al., *Anxiety and depression are related to dyspnea and clinical control but not with thoracoabdominal mechanics in patients with COPD.* Respir Physiol Neurobiol, 2015. **210**: p. 1-6.

122. von Leupoldt, A. and K. Kenn, *The psychology of chronic obstructive pulmonary disease.* Curr Opin Psychiatry, 2013. **26**(5): p. 458-63.
123. Hayen, A., M. Herigstad, and K.T. Pattinson, *Understanding dyspnea as a complex individual experience.* Maturitas, 2013. **76**(1): p. 45-50.
124. De Peuter, S., et al., *Dyspnea: the role of psychological processes.* Clin Psychol Rev, 2004. **24**(5): p. 557-81.
125. Esser, R.W., et al., *Brain Activation during Perception and Anticipation of Dyspnea in Chronic Obstructive Pulmonary Disease.* Front Physiol, 2017. **8**: p. 617.
126. Williams, M.T., et al., *Cognitive Behavioral Therapy for Management of Dyspnea: A Pilot Study.* Respir Care, 2015. **60**(9): p. 1303-13.
127. Ofir, D., et al., *Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2008. **177**(6): p. 622-9.
128. Faisal, A., et al., *Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders.* American Journal of Respiratory and Critical Care Medicine, 2016. **193**(3): p. 299-309.
129. Guenette, J.A., K.A. Webb, and D.E. O'Donnell, *Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD?* Eur Respir J, 2012. **40**(2): p. 322-9.
130. Laveneziana, P., et al., *Evolution of Dyspnea during Exercise in Chronic Obstructive Pulmonary Disease Impact of Critical Volume Constraints.* American Journal of Respiratory and Critical Care Medicine, 2011. **184**(12): p. 1367-1373.
131. Jolley, C.J., et al., *Neural respiratory drive and breathlessness in COPD.* Eur Respir J, 2015. **45**(2): p. 355-64.
132. O'Donnell, D.E., A.L. Hamilton, and K.A. Webb, *Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD.* Journal of Applied Physiology, 2006. **101**(4): p. 1025-1035.
133. Ekstrom, M., et al., *Absolute values of lung function explain the sex difference in breathlessness in the general population.* Eur Respir J, 2017. **49**(5).
134. Ekstrom, M., et al., *Absolute lung size and the sex difference in breathlessness in the general population.* PLoS One, 2018. **13**(1): p. e0190876.
135. Ofir, D., et al., *Sex differences in the perceived intensity of breathlessness during exercise with advancing age.* J Appl Physiol (1985), 2008. **104**(6): p. 1583-93.
136. Schaeffer, M.R., et al., *Physiological mechanisms of sex differences in exertional dyspnoea: role of neural respiratory motor drive.* Exp Physiol, 2014. **99**(2): p. 427-41.
137. Ekstrom, M., et al., *Spirometric Volumes and Breathlessness Across Levels of Airflow Limitation: The COPDGene Study.* Am J Respir Crit Care Med, 2018.
138. Smith, A.K., et al., *Prevalence and Outcomes of Breathlessness in Older Adults: A National Population Study.* J Am Geriatr Soc, 2016. **64**(10): p. 2035-2041.
139. Currow, D.C., et al., *The independent association of overweight and obesity with breathlessness in adults: a cross-sectional, population-based study.* Eur Respir J, 2017. **50**(3).

140. Bowden, J.A., et al., *Predictors of chronic breathlessness: a large population study.* BMC Public Health, 2011. **11**: p. 33.
141. Mahler, D.A., et al., *American College of Chest Physicians Consensus Statement on the Management of Dyspnea in Patients With Advanced Lung or Heart Disease.* Chest, 2010. **137**(3): p. 674-691.
142. Marciniuk, D.D., et al., *Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guideline.* Canadian Respiratory Journal, 2011. **18**(2): p. 69-78.
143. Vogelmeier, C.F., et al., *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary.* Am J Respir Crit Care Med, 2017. **195**(5): p. 557-582.
144. Qaseem, A., et al., *Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society.* Ann Intern Med, 2011. **155**(3): p. 179-91.
145. Ekstrom, M.P., A.P. Abernethy, and D.C. Currow, *The management of chronic breathlessness in patients with advanced and terminal illness.* Bmj-British Medical Journal, 2015. **349**.
146. Higginson, I.J., et al., *An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial.* Lancet Respir Med, 2014. **2**(12): p. 979-87.
147. Coventry, P.A., *Does pulmonary rehabilitation reduce anxiety and depression in chronic obstructive pulmonary disease?* Curr Opin Pulm Med, 2009. **15**(2): p. 143-9.
148. Luckett, T., et al., *Contributions of a hand-held fan to self-management of chronic breathlessness.* Eur Respir J, 2017. **50**(2).
149. Galbraith, S., et al., *Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial.* J Pain Symptom Manage, 2010. **39**(5): p. 831-8.
150. Cranston, J.M., et al., *Domiciliary oxygen for chronic obstructive pulmonary disease.* Cochrane Database of Systematic Reviews, 2005(4).
151. Gorecka, D., et al., *Effect of long term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia.* Thorax, 1997. **52**(8): p. 674-679.
152. Ekstrom, M., et al., *Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review.* Annals of the American Thoracic Society, 2015. **12**(7): p. 1079-92.
153. Barnes, H., et al., *Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness.* Cochrane Database Syst Rev, 2016. **3**: p. CD011008.
154. Simon, S.T., et al., *Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults.* Cochrane Database Syst Rev, 2016. **10**: p. CD007354.

155. Currow, D.C., et al., *Sertraline in symptomatic chronic breathlessness: a double blind, randomised trial.* Eur Respir J, 2019. **53**(1).
156. Stoller, J.K., et al., *Oxygen Therapy for Patients With COPD Current Evidence and the Long-Term Oxygen Treatment Trial.* Chest, 2010. **138**(1): p. 179-187.
157. Croxton, T.L. and W.C. Bailey, *Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research: an NHLBI workshop report.* Am J Respir Crit Care Med, 2006. **174**(4): p. 373-8.
158. Ekstrom, M., et al., *A nationwide structure for valid long-term oxygen therapy: 29-year prospective data in Sweden.* Int J Chron Obstruct Pulmon Dis, 2017. **12**: p. 3159-3169.
159. Pepin, J.L., et al., *Long-term oxygen therapy at home. Compliance with medical prescription and effective use of therapy. ANTADIR Working Group on Oxygen Therapy. Association Nationale de Traitement a Domicile des Insuffisants Respiratories.* Chest, 1996. **109**(5): p. 1144-50.
160. *Swedish National Register for Respiratory Failure (Swedevox). Annual report. 2017. [Accessed 03 Mars 2019]. Available from: www.ucr.uu.se/swedevox/.*
161. O'Donnell, D.E., C. D'Arsigny, and K.A. Webb, *Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease.* American Journal of Respiratory and Critical Care Medicine, 2001. **163**(4): p. 892-898.
162. Uronis, H., et al., *Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease.* Cochrane Database of Systematic Reviews, 2011(6).
163. Ameer, F., et al., *Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest.* Cochrane Database of Systematic Reviews, 2014(6).
164. Jacobs, S.S., et al., *Patient Perceptions of the Adequacy of Supplemental Oxygen Therapy. Results of the American Thoracic Society Nursing Assembly Oxygen Working Group Survey.* Ann Am Thorac Soc, 2018. **15**(1): p. 24-32.
165. Arnold, E., et al., *Ambulatory oxygen: why do COPD patients not use their portable systems as prescribed? A qualitative study.* BMC Pulm Med, 2011. **11**: p. 9.
166. Ring, L. and E. Danielson, *Patients' experiences of long-term oxygen therapy.* J Adv Nurs, 1997. **26**(2): p. 337-44.
167. Tanash, H.A., F. Huss, and M. Ekstrom, *The risk of burn injury during long-term oxygen therapy: a 17-year longitudinal national study in Sweden.* International Journal of Chronic Obstructive Pulmonary Disease, 2015. **10**: p. 2479-2484.
168. Pattinson, K.T., et al., *Opioids depress cortical centers responsible for the volitional control of respiration.* J Neurosci, 2009. **29**(25): p. 8177-86.
169. Abdallah, S.J., et al., *Effect of morphine on breathlessness and exercise endurance in advanced COPD: a randomised crossover trial.* Eur Respir J, 2017. **50**(4).
170. Banzett, R.B., et al., *Using laboratory models to test treatment: morphine reduces dyspnea and hypercapnic ventilatory response.* Am J Respir Crit Care Med, 2011. **184**(8): p. 920-7.

171. Mahler, D.A., et al., *Endogenous opioids modify dyspnoea during treadmill exercise in patients with COPD.* Eur Respir J, 2009. **33**(4): p. 771-7.
172. Pattinson, K.T., *Opioids and the control of respiration.* Br J Anaesth, 2008. **100**(6): p. 747-58.
173. Rosenblum, A., et al., *Opioids and the treatment of chronic pain: controversies, current status, and future directions.* Exp Clin Psychopharmacol, 2008. **16**(5): p. 405-16.
174. Jennings, A.L., et al., *Opioids for the palliation of breathlessness in terminal illness.* Cochrane Database Syst Rev, 2001(4): p. CD002066.
175. Abernethy, A.P., et al., *Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea.* British Medical Journal, 2003. **327**(7414): p. 523-526.
176. Currow D, et al., *A phase III, multi-site, randomised, double blind, placebo controlled parallel arm study of daily extended release (ER) morphine for chronic breathlessness.* European Respiratory J, 2016. **48: OA4808**.
177. Currow D, et al., *Regular extended release morphine for chronic breathlessness: a multi-centre double-blind RCT.* European Respiratory J, 2018. **52: OA1624**.
178. Currow, D.C., et al., *Once-Daily Opioids for Chronic Dyspnea: A Dose Increment and Pharmacovigilance Study.* Journal of Pain and Symptom Management, 2011. **42**(3): p. 388-399.
179. Vozoris, N.T., et al., *Incident opioid drug use among older adults with chronic obstructive pulmonary disease: a population-based cohort study.* British Journal of Clinical Pharmacology, 2016. **81**(1): p. 161-170.
180. Ekstrom, M.P., et al., *Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study.* Bmj-British Medical Journal, 2014. **348**.
181. Janssen, D.J.A., et al., *Attitudes toward opioids for refractory dyspnea in COPD among Dutch chest physicians.* Chronic Respiratory Disease, 2015. **12**(2): p. 85-92.
182. Rocker, G., et al., *Perspectives of patients, family caregivers and physicians about the use of opioids for refractory dyspnea in advanced chronic obstructive pulmonary disease.* Canadian Medical Association Journal, 2012. **184**(9): p. E497-E504.
183. Light, R.W., et al., *Relationship between improvement in exercise performance with supplemental oxygen and hypoxic ventilatory drive in patients with chronic air-flow obstruction.* Chest, 1989. **95**(4): p. 751-756.
184. Woodcock, A.A., et al., *Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung-disease and normal blood-gases.* New England Journal of Medicine, 1981. **305**(27): p. 1611-1616.
185. Verberkt, C.A., et al., *Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis.* Eur Respir J, 2017. **50**(5).
186. Lundstrom, S., et al., *Developing a national quality register in end-of-life care: the Swedish experience.* Palliat Med, 2012. **26**(4): p. 313-21.

187. Emilsson, L., et al., *Review of 103 Swedish Healthcare Quality Registries.* J Intern Med, 2015. **277**(1): p. 94-136.
188. *The Swedish Register of Palliative Care, www.palliativ.se. (2013 Annual report) http://palliativ.se/wp-content/uploads/2014/03/SvenskaPalliatvregistret2014.pdf (accessed 1 Sept2014).*
189. Martinsson, L., et al., *Validation study of an end-of-life questionnaire from the Swedish Register of Palliative Care.* Acta Oncol, 2011. **50**(5): p. 642-7.
190. Brooke, H.L., et al., *The Swedish cause of death register.* Eur J Epidemiol, 2017. **32**(9): p. 765-773.
191. *World Health Organization. Manual of the International Classification of Diseases, Injuries and Causes of Death. 9th revision.* 1978, World Health Organization: Geneva, Switzerland.
192. *World Health Organization. Manual of the International Statistical Classification of Diseases and Health Related Problems. 10th revision.* 1992, World Health Organization: Geneva, Switzerland.
193. *The Causes of Death Register*. 2018 [cited 2018; Available from: http://www.socialstyrelsen.se/register/dodsorsaksregistret.
194. Sweden, S. *Causes of death*. 2008 [cited 2010 September 22]; Available from: http://www.socialstyrelsen.se/Publicerat/2008/10117/2008-42-6.htm.
195. Wettermark, B., et al., *The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months.* Pharmacoepidemiol Drug Saf, 2007. **16**(7): p. 726-35.
196. Wallerstedt, S.M., B. Wettermark, and M. Hoffmann, *The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature.* Basic Clin Pharmacol Toxicol, 2016. **119**(5): p. 464-469.
197. *The Swedish Prescribed Drug Register*. 2018 [cited 2018; Available from: http://www.socialstyrelsen.se/register/halsodataregister/lakemedelsregistret.
198. Higgins, J.P.T., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj-British Medical Journal, 2011. **343**.
199. *Global strategy for the diagnosis, management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease. 2017.* http://goldcopd.org.
200. Ahmadi, Z., et al., *End-of-life care in oxygen-dependent COPD and cancer: a national population-based study.* Eur Respir J, 2015. **46**(4): p. 1190-3.
201. Ahmadi, Z., et al., *Prescription of opioids for breathlessness in end-stage COPD: a national population-based study.* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 2651-2657.
202. Ekstrom, M., et al., *Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy.* Cochrane Database Syst Rev, 2016. **11**: p. CD006429.
203. Ahmadi, Z., et al., *Is chronic breathlessness less recognised and treated compared with chronic pain? A case-based randomised controlled trial.* Eur Respir J, 2018. **52**(3).
204. Edmonds, P., et al., *A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer.* Palliat Med, 2001. **15**(4): p. 287-95.

205. Claessens, M.T., et al., *Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments.* J Am Geriatr Soc, 2000. **48**(5 Suppl): p. S146-53.
206. Elkington, H., et al., *The healthcare needs of chronic obstructive pulmonary disease patients in the last year of life.* Palliat Med, 2005. **19**(6): p. 485-91.
207. Giacomini, M., et al., *Experiences of living and dying with COPD: a systematic review and synthesis of the qualitative empirical literature.* Ont Health Technol Assess Ser, 2012. **12**(13): p. 1-47.
208. Young, J., et al., *Using opioids to treat dyspnea in advanced COPD Attitudes and experiences of family physicians and respiratory therapists.* Canadian Family Physician, 2012. **58**(7): p. E401-E407.
209. Jennings, A.L., et al., *A systematic review of the use of opioids in the management of dyspnoea.* Thorax, 2002. **57**(11): p. 939-944.
210. Long-Term Oxygen Treatment Trial Research, G., et al., *A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation.* N Engl J Med, 2016. **375**(17): p. 1617-1627.
211. Ekstrom, M., et al., *Breathlessness measurement should be standardised for the level of exertion.* Eur Respir J, 2018. **51**(5).
212. Rocker, G.M., et al., *Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences andoutcomes.* CMAJ open, 2013. **1**(1): p. E27-36.
213. Hadjiphilippou, S., S.E. Odogwu, and P. Dand, *Doctors' attitudes towards prescribing opioids for refractory dyspnoea: a single-centred study.* BMJ Support Palliat Care, 2014. **4**(2): p. 190-192.
214. Edmonds, P., et al., *A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer.* Palliative Medicine, 2001. **15**(4): p. 287-295.
215. Smallwood, N., et al., *Integrated respiratory and palliative care may improve outcomes in advanced lung disease.* ERJ Open Res, 2018. **4**(1).
216. Rocker, G.M. and D. Cook, *'INSPIRED' approaches to better care for patients with advanced COPD.* Clin Invest Med, 2013. **36**(3): p. E114-20.
217. Ekstrom, M., et al., *One evidence base; three stories: do opioids relieve chronic breathlessness?* Thorax, 2018. **73**(1): p. 88-90.
218. Verberkt, C.A., et al., *A randomized controlled trial on the benefits and respiratory adverse effects of morphine for refractory dyspnea in patients with COPD: Protocol of the MORDYC study.* Contemp Clin Trials, 2016. **47**: p. 228-34.
219. Abernethy, A.P., et al., *Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial.* Lancet, 2010. **376**(9743): p. 784-793.
220. Perrault, H., et al., *Paced-walk and step tests to assess exertional dyspnea in COPD.* COPD, 2009. **6**(5): p. 330-9.
221. Sava, F., et al., *Detecting improvements in dyspnea in COPD using a three-minute constant rate shuttle walking protocol.* COPD, 2012. **9**(4): p. 395-400.

222. Borel, B., et al., *Three-minute constant rate step test for detecting exertional dyspnea relief after bronchodilation in COPD.* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 2991-3000.
223. Nishino, T., et al., *Inhaled furosemide greatly alleviates the sensation of experimentally induced dyspnea.* Am J Respir Crit Care Med, 2000. **161**(6): p. 1963-7.
224. Moosavi, S.H., et al., *Effect of inhaled furosemide on air hunger induced in healthy humans.* Respiratory Physiology & Neurobiology, 2007. **156**(1): p. 1-8.
225. Grogono, J.C., et al., *Inhaled furosemide for relief of air hunger versus sense of breathing effort: a randomized controlled trial.* Respir Res, 2018. **19**(1): p. 181.
226. Kohara, H., et al., *Effect of nebulized furosemide in terminally ill cancer patients with dyspnea.* J Pain Symptom Manage, 2003. **26**(4): p. 962-7.
227. Jensen, D., et al., *Mechanisms of dyspnoea relief and improved exercise endurance after furosemide inhalation in COPD.* Thorax, 2008. **63**(7): p. 606-613.

Paper I

End-of-life care in oxygen-dependent COPD and cancer: a national population-based study

To the Editor:

Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide [1], and is associated with high morbidity and poor symptom control for long periods of time as the disease progresses [2]. At the end of life, COPD patients have a symptom burden comparable to, and often greater than, that associated with cancer [3]. Comparison between COPD and cancer is relevant because cancer patients have well-established palliative care programmes. Despite having extensive and similar end-of-life (EOL) needs to cancer patients, studies report unrelieved symptoms and low referral rates to palliative care in advanced COPD patients [4].

Knowledge about symptoms and symptomatic treatments near death are vital to identify healthcare inequalities, and to identify ways to improve EOL care in advanced COPD. The aim of this study was to estimate the prevalence of symptoms and their management in the last week of life in people with oxygen-dependent COPD or cancer.

This was a nationwide, registry-based cohort study including all patients starting long-term oxygen therapy (LTOT) for physician-diagnosed COPD in the national Swedevox register who died between January 1, 2011 and October 14, 2013. The Swedevox register prospectively includes patients starting LTOT in Sweden with a population-based coverage of ∼85% [5]. Details of the register are described elsewhere [6].

Data on people with oxygen-dependent COPD were cross-linked using each patient's unique Swedish identification number with data in the Swedish Register of Palliative Care (SRPC). Patients in SRPC who died from cancer during the same time period were included as the comparator group. SRPC is a national quality register of the care of patients during their last week of life regardless of place of care or diagnosis, with a coverage of 87.4% of all cancer deaths nationwide in 2013 [7].

The SRPC collects data through an end-of-life questionnaire (ELQ) completed retrospectively by the responsible nurse and/or physician within a week of the patient's death, based on the patient record and experience of the care that may not have been documented, preferably after a team discussion, therefore including the experience of all team members. The ELQ includes data on the presence of breathlessness, pain, death rattle, nausea, anxiety and confusion, and prevalence of prescribing "as-needed" medications for pain, nausea, anxiety and death rattle during the last 7 days of life. A previous study supported the validity of the ELQ [8].

Prevalence was considered for each symptom in the questions of the ELQ: "Were any of the following symptoms prevalent at some time during the last week of life?" (yes or no). For any reported symptom, the level of symptom relief was graded as relieved, partially relieved or unrelieved. Prevalence of as-needed medication prescriptions was analysed among symptomatic patients for each identified symptom according to the question "Was medication prescribed for use 'as needed' in the form of injections before death for pain, death rattle, nausea and anxiety?" (yes or no).

The study was approved by local ethics committee (LundDNr 2013/379; University of Lund, Lund, Sweden). Statistical methods included standard descriptive statistics, t-tests and chi-square tests as appropriate, using Stata version 12 (StataCorp LP, College Station, TX, USA).

A total of 1128 COPD patients (mean±SD age 78±8 years at death; 60% women) and 56 843 cancer patients (age 75±12 years at death; 49% women) were included. Of LTOT patients from Swedevox, 59% were registered in SPRC and included in the study. Characteristics were similar between LTOT patients who were and were not included in terms of age, sex, lung function, body mass index and arterial blood gas levels, supporting the external validity of the study.

Compared with patients with cancer, COPD patients suffered from more breathlessness (73% *versus* 22%) and anxiety (63% *versus* 54%) but less pain (52% *versus* 81%) and nausea (11% *versus* 23%) during the last

week of life (figure 1a). COPD patients had lower rates of complete relief from breathlessness (22% *versus* 37%), anxiety (52% *versus* 61%) and death rattle (33% *versus* 44%) than cancer patients (figure 1b) ($p<0.001$ for all comparisons).

Prescription of as-needed medications during the last week of life was significantly lower in COPD than cancer for all symptoms: anxiety (76% *versus* 89%), death rattle (75% *versus* 88%), pain (80% *versus* 96%) and nausea (46% *versus* 77%) ($p<0.001$ for all comparisons). Furthermore, COPD patients had fewer as-needed medications prescribed to address specific symptoms when these were recorded: for anxiety (82% *versus* 95%), death rattle (89% *versus* 95%), pain (93% *versus* 97%) and nausea (64% *versus* 89%) ($p<0.001$ for all comparisons).

To evaluate the robustness of the findings, we compared symptom prevalence among patients for whom the symptom severity was rated according to the ELQ using a validated instrument. Results were similar for all symptoms, except that the relief of pain was higher in both groups, which supports the robustness of the findings.

Death was expected among 80% of COPD patients and 95% of cancer patients. However, COPD patients more often died in hospital (49% *versus* 28%) and received less specialised palliative home care (4% *versus* 14%). Fewer COPD patients had an EOL discussion (33% *versus* 61%) ($p<0.001$ for all comparisons).

Our study shows that patients with oxygen-dependent COPD suffered from a high symptom load with poor symptom control in the last week of life. Breathlessness was three times more common in oxygen-dependent COPD than cancer patients. Breathlessness was fully relieved for only 22% of patients. Prescription of as-needed medications for all symptoms was significantly lower among COPD patients than in patients with cancer.

These findings are in line with previous reports that COPD patients suffer from a high burden of symptoms, especially breathlessness, at the end of life [9]. We have expanded previous findings with data on prescription of palliative medications during the last week in advanced COPD specifically and comparing it with a cancer cohort that usually receives higher-quality EOL care.

Another finding is that COPD patients still have limited access to specialised care services and receive less palliative care than patients with cancer, consistent with previous reports [10, 11]. The limited specialised health and social care received by most COPD patients highlights the unequal distribution of specialised resources at the end of life depending on the underlying disease.

Strengths of the present study include its national population-based design, and inclusion of the largest cohort to date of patients with oxygen-dependent COPD and cancer. Few previous studies included the very last days of life and most studies were old or involved small cohorts [10, 12]. We report population-based, real-world data, and the findings probably have high external validity due to the national setup.

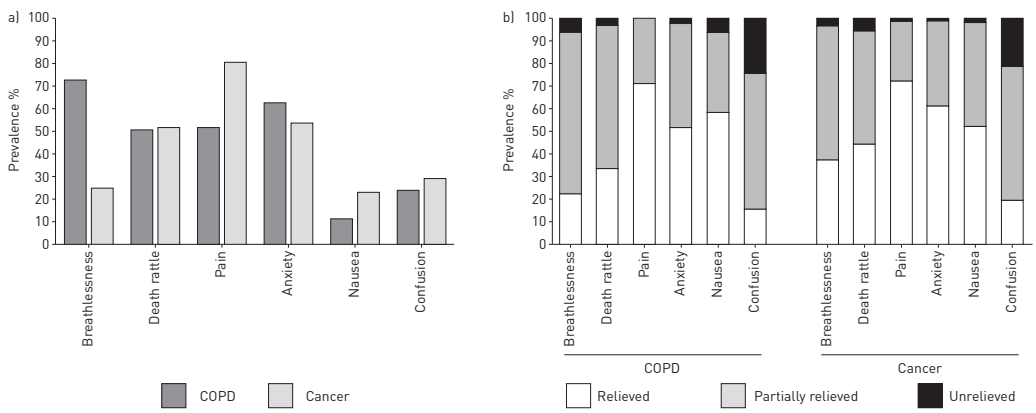


FIGURE 1 Patients with oxygen-dependent chronic obstructive pulmonary disease (COPD) (n=1128) or cancer (n=56 843). The prevalence of a) symptoms, and b) relieved, partially relieved and unrelieved symptoms in symptomatic patients during the last week of life in Sweden.

Limitations of our study include that data on palliative care in SRPC were collected retrospectively. The difficulties of predicting the prognosis in advanced COPD would make prospective data collection near death problematic among severely ill patients. The ELQ was answered by staff, which could be affected by recall or reporting bias. However, staff proxy assessments of symptoms in patients with advanced disease might be a valid alternative, especially for the detection of breathlessness [13].

For clinicians, this study highlights the need for adequate EOL care among patients with advanced COPD. This includes symptom management, the need for integrated respiratory and palliative care, and increased access to specialised palliative care services [14]. Breathlessness is very common in advanced COPD and poor symptom control remains a significant problem before death. At present, there is substantial evidence in favour of treatment with opioids, as randomised trials have shown that oral sustained-release morphine can relieve chronic refractory breathlessness [15]. A recent study by our group supports the safety of low-dose opioids in severe COPD [16].

In conclusion, this study identifies areas for improvement of the quality of EOL care received by COPD patients. Further engagement of health service providers and policy makers is necessary in order to provide these patients with equal and decent EOL care.

@ERSpublications
COPD patients have a high symptom burden but receive less palliative care than cancer patients at the end of life http://ow.ly/NchLv

Zainab Ahmadi[1], Staffan Lundström[2,3], Christer Janson[4], Peter Strang[2,3], Margareta Emtner[4], David C. Currow[5] and Magnus Ekström[1,5]
[1]Department of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University Hospital, Lund, Sweden. [2]Palliative Care Services, Stockholms Sjukhem Foundation, Stockholm, Sweden. [3]Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden. [4]Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden. [5]Discipline, Palliative and Supportive Services, Flinders University, Adelaide, Australia.

Correspondence: Zainab Ahmadi, Department of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University Hospital, SE- 221 00 Lund, Sweden. E-mail: zai.ahmd@gmail.com

Received: Jan 19 2015 | Accepted after revision: May 16 2015 | First published online: August 6 2015

Conflict of interest: None declared.

Support statement: This study was funded by the Swedish Society of Medicine, the Swedish Respiratory Society, the Scientific Committee of Blekinge County Council, the Wera and Emil Cornell Foundation, and the Swedish Heart-Lung Foundation.

Acknowledgements: The work was carried out at the Department of Respiratory Medicine, Blekinge Hospital, Karlskrona, and Lund University, Lund, Sweden. We thank Bengt Midgren (Department of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University Hospital, Lund, Sweden) for his valuable insights, Greger Fransson (Palliative Care Services, Stockholms Sjukhem Foundation, Stockholm, Sweden) for database management, and all the physicians and nurses who collected the data and cared for the patients.

References

1 Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095–2128.
2 Currow DC, Smith J, Davidson PM, *et al.* Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study. *J Pain Symptom Manage* 2010; 39: 680–690.
3 Bausewein C, Booth S, Gysels M, *et al.* Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer. *J Palliat Med* 2010; 13: 1109–1118.
4 Luddington L, Cox S, Higginson I, *et al.* The need for palliative care for patients with non-cancer diseases: a review of the evidence. *Int J Palliat Nurs* 2001; 7: 221–226.
5 Strom K, Boe J. A national register for long-term oxygen therapy in chronic hypoxia: preliminary results. *Eur Respir J* 1988; 1: 952–958.
6 Ekstrom MP, Hermansson AB, Strom KE. Effects of cardiovascular drugs on mortality in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187: 715–720.
7 The Swedish Register of Palliative Care. Årsrapport för Svenska Palliativregistret verksamhetsåret 2013 [Annual report of the Swedish Register of Palliative Care for the fiscal year 2013]. http://palliativ.se/wp-content/uploads/2014/03/SvenskaPalliatvregistret2014.pdf Date last accessed: September 1, 2014. Date last updated: 2014.
8 Martinsson L, Heedman PA, Lundstrom S, *et al.* Validation study of an end-of-life questionnaire from the Swedish Register of Palliative Care. *Acta Oncol* 2011; 50: 642–647.
9 Moens K, Higginson IJ, Harding R. Are there differences in the prevalence of palliative care-related problems in people living with advanced cancer and eight non-cancer conditions? A systematic review. *J Pain Symptom Manage* 2014; 48: 660–77.

10 Edmonds P, Karlsen S, Khan S, *et al.* A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer. *Palliat Med* 2001; 15: 287–295.
11 Elkington H, White P, Addington-Hall J, *et al.* The healthcare needs of chronic obstructive pulmonary disease patients in the last year of life. *Palliat Med* 2005; 19: 485–491.
12 Claessens MT, Lynn J, Zhong Z, *et al.* Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *J Am Geriatr Soc* 2000; 48: Suppl., S146–S153.
13 Simon ST, Altfelder N, Alt-Epping B, *et al.* Is breathlessness what the professional says it is? Analysis of patient and professionals' assessments from a German nationwide register. *Support Care Cancer* 2014; 22: 1825–1832.
14 Higginson IJ, Bausewein C, Reilly CC, *et al.* An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014; 2: 979–987.
15 Abernethy AP, Currow DC, Frith P, *et al.* Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ* 2003; 327: 523–528.
16 Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, *et al.* Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014; 348: g445.

Eur Respir J 2015; 46: 1190–1193 | DOI: 10.1183/09031936.00035915 |

The end of life (EOL) questionnaire from 2011 01 01

The Swedish Palliative Register Form to be filled out in connection with the death of a person.

To be filled in by the responsible doctor or nurse. All reports are to be submitted through www.palliativ.se

1. Unit code _____ (received at registration of participation through the website www.palliativ.se)

2. Social insurance identification number_____

3. Name of the deceased_____ (used first name and surname)

4. Date of death_____

5. Date of admission to the unit where death occurred (for primary care/home care = "active home care")_____

6. The place of death is best described as a:
   - o Nursing home
   - o Short-term care home
   - o Hospital ward – not palliative
   - o Hospice/palliative hospital ward
   - o Own home, with support from specialized palliative home care
   - o Own home, with support from basal home care
   - o Other_____

7. Main disease that caused death:
   - o Cancer
   - o Heart disease
   - o Lung disease
   - o Dementia
   - o Stroke
   - o Other neurological disease
   - o Diabetes
   - o Post-fracture condition
   - o Multimorbidity
   - o Other, namely_____

8. Will a forensic autopsy be performed?
   - o Yes, forensic autopsy
   - o Yes, clinical autopsy
   - o No

If the answer is Yes, forensic autopsy – answer only question 28-30.
If the answer is NO or Yes, clinical autopsy – continue to question 9.

9. According to the deceased's medical history, death was

- Expected
- Not expected
- Don't know

If the answer is Yes or Don't Know, answer all the following questions.
If the answer to NO, answer only question 14, 16, 18, 28-30.

10. How long before death did the patient/person receiving care loose his/her ability of self-determination?
- Preserved ability until death.
- Hours
- Days
- Weeks
- Months or more
- Don't know

11. Has an informing "breakpoint" conversation from a doctor with the patient about impending death taken place, during the last period in life?
- Yes
- No
- Don't know

12. Did the place of death correspond with the person receiving care's/patient's latest spoken wish?
- Yes
- No
- Don't know

13 a. Did the person receiving care/patient had pressure ulcers before coming to the unit (mark the highest grade of pressure ulcer)?
- Yes, Grade 1
- Yes, Grade 2
- Yes, Grade 3
- Yes, Grade 4
- No
- Don't know

If the answer is Yes (Grade 1-4), answer question 13b.
If the answer is No or Don't Know, continue to question 14 a.

13b. Was the pressure ulcer documented?
- Yes
- No
- Don't know

14 a. Did the person receiving care/patient die with pressure ulcer (mark the highest grade of pressure ulcer)?
- Yes, Grade 1
- Yes, Grade 2
- Yes, Grade 3
- Yes, Grade 4
- No

- Don’t know

If the answer is Yes (Grade 1-4), answer question 14b.
If the answer is No or Don’t Know, continue to question 15 a.

14b. Was the pressure ulcer documented?
- Yes
- No
- Don’t know

15 a. Did the person receiving care/patient have oral health inspection during the last week of life?
- Yes
- No
- Don’t know

If the answer is Yes, answer question 15b.
If the answer is No or Don’t Know, continue to question 16.

15 b. At the inspection of oral health, any abnormal findings that were noticed?
- Yes
- No
- Don’t know

If the answer is Yes, answer question 15c.
If the answer is No or Don’t Know, continue to question 16.

15c. Was the oral health inspection documented?
- Yes
- No
- Don’t know

16. Was there anyone present at the moment of death?
- Yes, Next of kin
- Yes, Next of kin and Staff
- Yes, Staff
- No one
- Don’t know

17. Has an informing “breakpoint” conversation from a doctor with the patient’s next of kin about the about the impending death of the patient and that the care was focused on improving quality of life and symptom management, taken place during the last period in life?
- Yes
- No
- Don’t know
- No Next of kin.

18. Have the next of kin had or will they be offered a follow-up appointment 1-2 months after death?
- Yes
- No
- Don’t know
- No Next of kin.

19. Did the person receiving care/patient had parenteral fluids or nasogastric tube feeding of fluids or nutrition during the last day of life?

- Yes
- No
- Don't know

20. Were any of the following symptoms (20 a-f) prevalent at some time during the last week of life?

20a. Pain

- Yes
- No
- Don't know

If the answer is Yes, answer the following question.
If the answer is No or Don't Know, continue to question 20b.
Relief from pain:

- Relieved
- Partially relieved
- Unrelieved

20b. Death rattle

- Yes
- No
- Don't know

If the answer is Yes, answer the following question.
If the answer is No or Don't Know, continue to question 20c.
Relief from death rattle:

- Relieved
- Partially relieved
- Unrelieved

20c. Nausea

- Yes
- No
- Don't know

If the answer is Yes, answer the following question.
If the answer is No or Don't Know, continue to question 20d.
Relief from nausea:

- Relieved
- Partially relieved
- Unrelieved

20d. Anxiety

- Yes
- No
- Don't know

If the answer is Yes, answer the following question.
If the answer is No or Don't Know, continue to question 20e.
Relief from anxiety:

- Relieved
- Partially relieved
- Unrelieved

20e. Breathlessness
- Yes
- No
- Don't know

If the answer is Yes, answer the following question.
If the answer is No or Don't Know, continue to question 20f.
Relief from breathlessness:
- Relieved
- Partially relieved
- Unrelieved

20f. Confusion
- Yes
- No
- Don't know

If the answer is Yes, answer the following question.
If the answer is No or Don't Know, continue to question 21.
Relief from confusion:
- Relieved
- Partially relieved
- Unrelieved

21. Have a VAS, NRS scale or another validated scale for pain assessment been used for evaluation of pain during the last week of the patient's life?
- Yes
- No
- Don't know

22. Did the person receiving care/patient had severe pain during the last week of life (for example VAS>6 or severe pain according to another validated scale for pain assessment)?
- Yes
- No
- Don't know

23. Have a VAS, NRS scale or another validated scale for symptom assessment been used for evaluation of patients other symptoms during the last week of the patient's life?
- Yes
- No
- Don't know

24. Was medication prescribed for use as needed in the form of injections before death, for:
- Opioids for pain
  - Yes
  - No
  - Don't know
- Death rattle

- Yes
- No
- Don’t know

- Nausea
  - Yes
  - No
  - Don’t know
- Anxiety
  - Yes
  - No
  - Don’t know

25. How long time before death, did a doctor visit/examine the patient/person receiving care?
    - Days
    - Weeks
    - Months or more
    - Don’t know

26. Has special competence outside the team/ward been consulted regarding the patient’s not completely alleviated symptoms?
    - Yes, pain unit
    - Yes, palliative team
    - Yes, other hospital unit
    - Yes, paramedics
    - Yes, spiritual representative
    - No
    - Don’t know

27. Are you content with the end-of- life care provided for the person receiving care/patient?
    - 1 (Not at all)
    - 2
    - 3
    - 4
    - 5 (Completely)

28. Date the questions were answered _____

29. The questionnaire is answered by
    - Single staff
    - In a group

30. Responsible informant (name) _____
    - Doctor
    - Nurse
    - Other staff

E-mail address_____

Paper II

International Journal of COPD

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Prescription of opioids for breathlessness in end-stage COPD: a national population-based study

Zainab Ahmadi[1,2]
Eva Bernelid[2]
David C Currow[3]
Magnus Ekström[1–3]

[1]Department of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University Hospital, Lund, [2]Department of Medicine, Blekinge Hospital, Karlskrona, Sweden; [3]Discipline, Palliative and Supportive Services, Flinders University, Adelaide, SA, Australia

Background: Low-dose opioids can relieve breathlessness but may be underused in late-stage COPD due to fear of complications, contributing to poor symptom control.

Objectives: We aimed to study the period prevalence and indications of opioids actually prescribed in people with end-stage COPD.

Methods: The study was a longitudinal, population-based study of patients starting long-term oxygen therapy (LTOT) for COPD between October 1, 2005 and June 30, 2009 in Sweden. A random sample (n=2,000) of their dispensed opioid prescriptions was obtained from the national Prescribed Drugs Register from 91 days before starting LTOT until the first of LTOT withdrawal, death, or study end (December 31, 2009). We analyzed medication type, dispensed quantity, date of dispensing, and indications categorized as pain, breathlessness, other, or unknown.

Results: In total, 2,249 COPD patients (59% women) were included. During a median follow-up of 1.1 (interquartile range 0.6–2.0) years, 1,034 patients (46%) were dispensed ≥1 opioid prescription (N=13,722 prescriptions). The most frequently prescribed opioids were tramadol (23%), oxycodone (23%), morphine (16%), and codeine (16%). Average dispensed quantity was 9.3 (interquartile range 3.7–16.7) defined daily doses per prescription. In the random sample, the most commonly stated indication was pain (97%), with only 2% for breathlessness and 1% for other reasons.

Conclusion: Despite evidence that supported the use of opioids for the relief of breathlessness predating this study, opioids are rarely prescribed to relieve breathlessness in oxygen-dependent COPD, potentially contributing to less-than-optimal symptom control. This study creates a baseline against which to compare future changes in morphine prescribing in this setting.

Keywords: COPD, symptoms, breathlessness, opioids, prescriptions, LTOT

Introduction

COPD is a leading cause of mortality worldwide, and is associated with high burden of symptoms, often poorly controlled in advanced disease stages.[1–4] The prevalence and severity of breathlessness are higher in end-stage COPD than in advanced lung cancer, both during the final year of life and in the terminal weeks and days near death.[5,6] Despite long-term oxygen therapy (LTOT), most COPD patients suffer from breathlessness at rest or on minimal exertion that greatly limits even the basic activities of daily living.[7–9] Breathlessness that persists at rest or on minimal exertion despite optimal treatment of the underlying disease(s) is termed "refractory breathlessness."[10,11]

Opioids have a growing evidence base for decreasing refractory breathlessness in advanced COPD.[10,12] Jennings et al concluded in a Cochrane meta-analysis that

Correspondence: Zainab Ahmadi
Department of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University Hospital, Klinikgatan 18, SE-221 00 Lund, Sweden
Tel +46 46 17 1000
Email zai.ahmd@gmail.com

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/COPD.S112484

low doses of oral sustained-release morphine can reduce chronic refractory breathlessness,[12] which was confirmed by an adequately powered crossover trial in 2003.[10]

Clinicians may, however, be reluctant to prescribe opioids due to a fear of adverse events including confusion, falls, and respiratory depression in patients with respiratory compromise.[13] Among stable outpatients with advanced COPD, 94% reported moderate to severe breathlessness but only 2% used opioids, such as morphine.[13] In palliative care, only one-fourth of COPD patients received opioids during their last 6 months of life, compared to half of the patients with lung cancer.[14]

No study has evaluated the indications for actual prescribed opioids, and data are limited on the temporal trends and prescription as death approaches. A recent study reported that opioid therapy, mostly short-term, was commonly used in COPD but did not analyze the indications for opioid use.[15] Underuse of opioids for breathlessness in severe COPD could contribute to insufficient symptom control and unnecessary suffering.

The aim of this study was to evaluate the indications, medication types, and temporal patterns of opioid prescription in severe oxygen-dependent COPD.

Materials and methods

Design and participants

This was an observational, population-based study of patients aged 45 years or older who started LTOT for COPD in the Swedish Register for Respiratory Failure between October 1, 2005 and June 30, 2009. The database was used in a recent safety study of opioids.[16]

Data sources

The Swedish Register for Respiratory Failure prospectively includes patients starting LTOT in Sweden with a nationwide coverage of approximately 85%.[17] It contains physiological data including arterial blood gas tensions when breathing air and oxygen, body mass index, World Health Organization (WHO) performance status,[18] and forced expiratory volume in 1 second registered at the start of LTOT. Details of the register have been published.[19]

Data on all dispensed outpatient prescriptions were obtained from the Swedish Prescribed Drugs Register[20] during the study period, which was from 91 days before the start of LTOT until the first of LTOT withdrawal, death, or study end (December 31, 2009). Drugs were categorized according to the Anatomical Therapeutic Chemical Classification System (ATC codes) as previously described.[16] Vital status was obtained from the Swedish Causes of Death Register.

Opioid prescriptions

A random sample (n=2,000) of the cohort's dispensed opioid prescriptions during the study period was derived from the database using the commando runiform in the statistical package Stata, version 13 (StataCorp LP; College Station, TX, USA). The random sample was analyzed in relation to medication type, dispensed quantity as WHO defined daily doses,[21] date of dispensing, and free-text indication. Each indication was reviewed by a respiratory physician and categorized as pain, breathlessness, other, or unknown (insufficient information to identify an indication). Each prescription could have multiple indications and could include both a regular and an "as-needed" dose. In Sweden, the stated free-text indications are decided entirely by the prescribing physician and do not undergo external review by the pharmacy or clinic. Analysis of primary interest was the period prevalence of opioid prescriptions during the follow-up period.

Ethics

Participants provided their verbal consent when registered in Swedevox, and the consent procedure and the study were approved by the Lund University Research Ethics Committee (157/2007 and 350/2008), the Swedish National Board of Health and Welfare, and the Data Inspection Board.

Statistical analyses

Baseline characteristics were summarized as counts and percentages for categorical variables, mean values with standard deviation or median with interquartile range (IQR) or range for normally and nonnormally distributed continuous variables, respectively. Differences were tested using a *t*-test for continuous variables and chi-square test for unpaired categorical data. All tests were two sided, and statistical significance was defined as $P<0.05$. Statistical analyses were conducted using Stata version 12.1 (StataCorp LP, College Station, TX, USA).

Results

Participants

A total of 2,249 COPD patients (59% women) were included prospectively and followed-up for a median 1.1 years (IQR 0.6–2.0). During the study period, 1,034 patients (46 %) were dispensed at least one prescription of an opioid (in total 13,722 dispensed opioid prescriptions). As shown in Table 1, patients who were prescribed opioids were aged 74±8 years,

Table 1 Characteristics of oxygen-dependent COPD patients who were prescribed opioids

Characteristic	Total (n=1,034)	Patients with known indication for prescription (n=273)	Patients with unknown indication for prescription (n=302)
Age (years)	74.6±8	72.7±8	75.9±8
Females, n (%)	684 (66)	188 (69)	217 (72)
PaO_2 air (kPa)	6.6±0.87	6.7±0.86	6.4±0.86
$PaCO_2$ air (kPa)	6.3±1.2	6.3±1.1	6.4±1.2
WHO status, n (%)			
0	49 (5)	17 (6)	11 (4)
1	379 (37)	114 (42)	84 (28)
2	344 (33)	85 (31)	110 (36)
3	145 (14)	22 (8)	56 (18)
4	20 (2)	1 (0)	8 (3)
FEV_1 (L)	0.83±0.5	0.86±0.5	0.80±0.5
FEV_1 (% of predicted)	34±17.3	34±17.9	33±15.4
Follow-up (days)[a]	442 (231–754)	568 (262–834)	545 (268–749)

Notes: Data presented as mean ± SD unless stated otherwise. N (%) of missing for PaO_2, 146 (14); $PaCO_2$, 151 (15); WHO status, 97 (9); FEV_1, 403 (39); FEV_1 (% of predicted), 453 (44). [a]Median (first quartile–third quartile).
Abbreviations: FEV_1, forced expiratory volume in 1 second; PaO_2, arterial blood gas tension of oxygen on breathing air; $PaCO_2$, arterial blood gas tension of carbon dioxide on breathing air; SD, standard deviation; WHO, World Health Organization.

were mostly women (66%), and 70% were mostly ambulatory with WHO status 1–2 at LTOT start. The random sample of 2,000 (15%) of the opioid prescriptions was dispensed by 575 patients.

Types of opioids

The most frequently prescribed opioids were tramadol (23%), oxycodone (23%), morphine (16%), and codeine (16%), as shown in Table 2. The average dispensed quantity was 9.3 (IQR 3.7–16.7) defined daily doses per prescription. Of the opioid prescriptions, 417 (21%) included an as-needed dose (Table 2). No nebulized opioids were prescribed. The indication was present in 33% (n=662) of the opioid prescriptions and absent in 67% (n=1338) of the opioid prescriptions (Table 3). Characteristics were similar between the patients whose indications for opioids were known compared to those with unknown indications (Table 1).

Table 2 Opioid prescriptions in oxygen-dependent COPD

Prescriptions	Random sample n=2,000
Substance, n (%)	
Codeine	318 (16)
Dextropropoxifen	270 (14)
Fentanyl	99 (5)
Morphine	314 (16)
Oxycodone	449 (22)
Tramadol	459 (23)
Others	91 (4)
DDDs per prescription[a]	9.3 (3.7–16.7)
Included "as-needed" dose, n (%)	417 (21)

Notes: A random sample of 2,000 (15%) of the total 13,722 opioid prescriptions was analyzed regarding medication type, dispensed amount, date of dispensation, and indication (free text). [a]Median (first quartile–third quartile).
Abbreviation: DDDs, defined daily doses.

Temporal patterns of indications

Table 3 shows indications for the prescriptions of opioids before and after the start of LTOT. The vast majority of the stated indications were pain (97%), with only 2% for breathlessness and 1% for other reasons among the prescriptions with known indications. Prescriptions with dual indications (pain and breathlessness) occurred in only 0.7% (n=5) of the known indications. During the last 6 months of the patients' lives, the period prevalence of opioid prescriptions for breathlessness was only 4% (Table 4).

Opioids were prescribed predominantly among patients with WHO performance status 1–2 (Table 5).

Figure 1 shows the temporal pattern of opioid prescriptions during follow-up by indication. Pain was the predominant indication throughout the study period. Breathlessness as an indication increased slightly during follow-up but the absolute numbers were low.

Discussion

Key findings

In oxygen-dependent COPD, breathlessness was an indication in less than 2% of opioid prescriptions and only 4% in the last 6 months of life. Among patients, 46% took an opioid during follow-up. Of the stated indications, the vast majority was pain (97%) and as many as 67% of opioid prescriptions lacked any information on the indication.

Table 3 Indications of 2,000 random opioid prescriptions among 575 patients with oxygen-dependent COPD

Indication, n (%)	Overall	6 months before LTOT	First 6 months of LTOT	Last 6 months of LTOT
Known indication	662 (33)	153 (39)	188 (37)	215 (30)
Pain	642 (97)	150 (98)	183 (97)	206 (96)
Breathlessness	13 (2)	1 (0.7)	4 (2)	6 (3)
Other	7 (1)	2 (1)	1 (0.5)	3 (1)
Unknown indication	1,338 (67)	236 (61)	325 (63)	508 (70)

Note: Percentages might not sum to 100 because of rounding.
Abbreviation: LTOT, long-term oxygen therapy.

Strengths and limitations

Strengths of the present study include its national population-based design with complete longitudinal data on all dispensed outpatient opioid prescriptions and vital status nationwide. National registry data enabled complete follow-up in these frail patients with advanced disease. The use of a randomized prescription sample enabled analysis of the free-text indications, and the timing of prescription was analyzed in relation to LTOT and death.

A possible limitation was that a high proportion of prescriptions lacked a stated indication. This would probably not lead to bias because the opioid indication is not externally reviewed and does not affect the price or the patient's ability to dispense the opioid prescription in Sweden. It also reflects clinical reality and is an important finding in its own right by identifying an area of possible improvement in clinical practice. Clear information regarding the indication and aim of the treatment should be written on all prescriptions, especially regarding sick elderly patients and when informal caretakers are involved. Prescription data did not include opioids given in hospital, but this is unlikely to substantially change the relations between the treatment indications. Another possible limitation is that the study included data between 2005 and 2009. However, evidence that supported the use of opioids for the relief of breathlessness was already available from a Cochrane meta-analysis published in 2002[12] and an adequately powered trial published in 2003.[10] We did not have patient-reported data including breathlessness or quality of life scores to further characterize patients in this study.

Table 4 Prescribed opioids at LTOT start versus before death in oxygen-dependent COPD patients who died (n=278)

Indication, n (%)	First 6 months of LTOT	Last 6 months of life
Known indication	75 (28)	106 (29)
Pain	71 (95)	101 (95)
Breathlessness	3 (4)	4 (4)
Other	1 (1)	1 (1)
Unknown indication	191 (72)	265 (71)

Abbreviation: LTOT, long-term oxygen therapy.

Given the evidence of the efficacy of opioids for breathlessness,[10,12,16,22] the study design, and the striking difference in prescribing for pain (97% of prescriptions) and breathlessness (2%), the finding that opioids are rarely used for refractory breathlessness in advanced and end-stage COPD likely has high validity.

Relation to current evidence

Patients with advanced and oxygen-dependent COPD are known to suffer from high levels of breathlessness despite LTOT, both in outpatients and at the end of life.[6–9] Opioids have been reported to be less prescribed near death in advanced COPD than in lung cancer, despite the presence of more breathlessness in COPD and similar rates of pain.[6,14]

The current findings are consistent with a Dutch study that chest physicians rarely prescribed opioids for refractory breathlessness to outpatients with advanced COPD.[23] The most frequent barriers to opioid prescription were the physician's fear of possible serious adverse events, including respiratory depression and resistance of some patients.[23] Although more research is needed, the evidence to date supports the safety of low-dose opioids for symptomatic treatment in advanced diseases including COPD. This evidence consists of a Cochrane meta-analysis,[12] a systematic review,[24] a randomized trial,[10] and several studies.[16,22] Sustained-release morphine should be considered as a first line treatment and should be initiated at a low dose regularly and titrated upward over days and weeks, balancing beneficial and adverse effects.[25,26] All treatments assume adequate follow-up of the patient's clinical condition and symptoms, including proper prophylaxis and treatment for expected effects such as opioid-related constipation.[10,25] Opioid side effects include initial nausea, worsened constipation, or dizziness, which have been reversible upon dose reduction or discontinuation.[16] There have been no reported serious adverse events related to titrated low-dose opioids,

Table 5 Indications of opioid prescriptions by WHO performance status in oxygen-dependent COPD

Indication, n (%)	WHO status 0	WHO status 1	WHO status 2	WHO status 3	WHO status 4
Known indication	38 (45)	273 (42)	224 (32)	55 (17)	2 (7)
Pain	38 (100)	269 (99)	211 (94)	53 (96)	2 (100)
Breathlessness	0	2 (0.7)	8 (4)	2 (4)	0
Other	0	2 (0.7)	5 (2)	0	0
Unknown indication	47 (55)	374 (58)	485 (68)	275 (83)	28 (93)

Notes: Percentages might not sum to 100 because of rounding. WHO status: 0, fully active, able to carry out all pre-disease activities without restriction; 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work; 2, ambulatory and capable of all selfcare but unable to carry out any work activities, and up and about more than 50% of waking hours; 3, capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4, completely disabled, incapable of any selfcare, totally confined to bed or chair.
Abbreviation: WHO, World Health Organization.

including no case of respiratory depression.[12,16,22,24] A study using the present database found that low-dose opioids were not associated with increased rates of hospitalization or death in patients with severe oxygen-dependent COPD.[16] In a pharmacovigilance study of 83 patients who received 10–30 mg oral morphine per day, no episodes of respiratory depression or hospitalizations were reported up to 3 months.[22] A recent meta-analysis (16 studies; 271 patients) reported that opioids safely improved breathlessness in severe COPD.[24] The findings from this meta-analysis are consistent with those of Jennings et al.[12] Rocker et al reported that patients experienced beneficial effects from opioid therapy for breathlessness that sustained over months.[27] The present study suggests that, despite the high symptom burden[6] and the available safety data,[12,16,22,24] there is a widespread reluctance to prescribe opioids for breathlessness in advanced COPD.

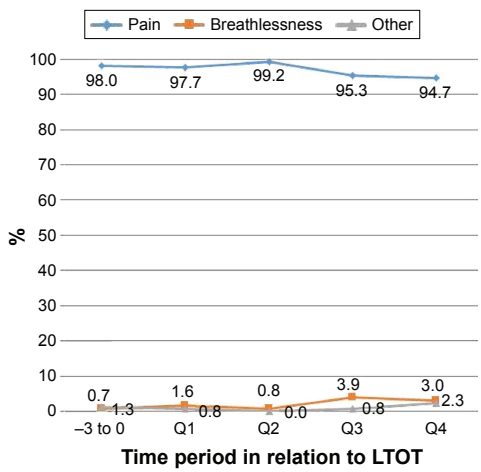


Figure 1 Trend for stated indications of opioid prescriptions in 575 patients with oxygen-dependent COPD.
Notes: Percentage of dispensed opioid prescriptions with the indication for pain, breathlessness, or other (of the prescriptions with known indication; N=662; 33%). Time periods are 3 months before starting LTOT (–3 to 0 months), and each quartile (Q1–Q4) of follow-up during LTOT.

What this study adds

This is, to the authors' knowledge, the first study looking at the indications for prescribing opioids in severe COPD. This study shows that patients with oxygen-dependent COPD are treated with opioids; 46% of patients were dispensed at least one prescription during follow-up. Pain was the dominating opioid indication (97%), and breathlessness was the indication in only 2% of the prescriptions. Although breathlessness as an indication increased, slightly during follow-up, absolute numbers were low and during the last 6 months of life, only 4% of opioid prescriptions were for breathlessness. These findings further support undertreatment of breathlessness both for symptom relief and at the end of life.[6]

Implications and the future

This study forms a crucial baseline against which to evaluate temporal trends in opioid prescribing for COPD as the evidence base continues to evolve. Research is needed to inform and implement evidence-based opioid treatment for the relief of refractory breathlessness in severe COPD. Large-scale longitudinal studies are needed to evaluate adverse effects and the net clinical benefit of opioids in clinical practice.[16,28] Initiatives for implementing evidence-based treatment for symptom relief are warranted in severe respiratory diseases.

For clinicians, this study identifies potential improvement opportunities in the management of chronic refractory breathlessness. Changing the threshold at which people experience breathlessness is likely to have important implications for activities of daily living. It is likely that people exert themselves to the same level of breathlessness, and if this takes longer or more intense exertion to reach, then people are likely to be more active, therefore breaking the cycle of deconditioning. Structured measurement of

the breathlessness severity in routine care is important in evidence-based symptomatic treatment.[29] Given their growing evidence of efficacy and safety, low-dose opioids, after careful initiation and titration, can be prescribed with better confidence for the relief of refractory breathlessness in advanced COPD.[30,31] Another important finding is that more than half of the opioid prescriptions lacked any written indication. Clear oral and written information on why opioid is given and on the aim of the therapy is likely important for the safety of the therapy, compliance, and symptom control in these often elderly, frail, and often multi-morbid patients with end-stage respiratory diseases.

Conclusion

In severe oxygen-dependent COPD, almost half of patients were treated with opioids at some point, largely for pain (97%). Breathlessness was a rare indication for opioids (2%), even near death.

Acknowledgments

We thank all the physicians and nurses who collected the data and cared for the patients. This study was funded by unrestricted grants from the Scientific Committee of Blekinge County Council, Swedish Society of Medicine, Swedish Respiratory Society, Swedish Heart-Lung Foundation, and the Wera and Emil Cornell Foundation.

Author contributions

ME had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. DCC, ME, and ZA conceptualized and designed the study; EB and ME were responsible for the acquisition of the data; EB, ME, and ZA analyzed the data; DCC, ME, and ZA interpreted the data; ME and ZA drafted the article; and DCC, EB, ME, and ZA revised important intellectual content and approved the version to be published.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380(9859):2095–2128.
2. Walke LM, Byers AL, Tinetti ME, Dubin JA, McCorkle R, Fried TR. Range and severity of symptoms over time among older adults with chronic obstructive pulmonary disease and heart failure. *Arch Intern Med*. 2007;167(22):2503–2508.
3. Johnson MJ, Bowden JA, Abernethy AP, Currow DC. To what causes do people attribute their chronic breathlessness? A population survey. *J Palliat Med*. 2012;15(7):744–750.
4. Müllerová H, Lu C, Li H, Tabberer M. Prevalence and burden of breathlessness in patients with chronic obstructive pulmonary disease managed in primary care. *PLoS One*. 2014;9(1):e85540.
5. Moens K, Higginson IJ, Harding R. EURO IMPACT. Are There differences in the prevalence of palliative care-related problems in people living with advanced cancer and eight non-cancer conditions? A systematic review. *J Pain Symptom Manage*. 2014;48(4):660–677.
6. Ahmadi Z, Lundström S, Janson C, et al. End-of-life care in oxygen-dependent COPD and cancer: a national population-based study. *Eur Respir J*. 2015;46(4):1190–1193.
7. Elkington H, White P, Addington-Hall J, Higgs R, Edmonds P. The healthcare needs of chronic obstructive pulmonary disease patients in the last year of life. *Palliat Med*. 2005;19(6):485–491.
8. Gulbas G, Gunen H, In E, Kilic T. Long-term follow-up of chronic obstructive pulmonary disease patients on long-term oxygen treatment. *Int J Clin Pract*. 2012;66(2):152–157.
9. Law S, Boyd S, Macdonald J, Raeside D, Anderson D. Predictors of survival in patients with chronic obstructive pulmonary disease receiving long-term oxygen therapy. *BMJ Support Palliat Care*. 2014. doi:10.1136/bmjspcare-2012-000432.
10. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ*. 2003;327(7414):523–528.
11. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185(4): 435–452.
12. Jennings AL, Davies AN, Higgins JP, Gibbs JS, Broadley KE. A systematic review of the use of opioids in the management of dyspnoea. *Thorax*. 2002;57(11):939–944.
13. Janssen DJ, Spruit MA, Uszko-Lencer NH, Schols JM, Wouters EF. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. *J Palliat Med*. 2011; 14(6):735–743.
14. Au DH, Udris EM, Fihn SD, McDonell MB, Curtis JR. Differences in health care utilization at the end of life among patients with chronic obstructive pulmonary disease and patients with lung cancer. *Arch Intern Med*. 2006;166(3):326–331.
15. Vozoris NT, Wang X, Fischer HD, et al. Incident opioid drug use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. *Br J Clin Pharmacol*. 2015;81(1):161–170.
16. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ*. 2014;348:g445.
17. Swedish National Register for Respiratory Failure (Swedevox). Annual Report. 2014. Available from: www.ucr.uu.se/swedevox/. Accessed October 9, 2015.
18. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982; 5(6):649–655.
19. Ekström MP, Hermansson AB, Strom KE. Effects of cardiovascular drugs on mortality in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(7):715–720.
20. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register – opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16(7):726–735.
21. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC Classification and DDD Assignment 2011*. WHO; 2010.
22. Currow DC, McDonald C, Oaten S, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage*. 2011;42(3):388–399.

23. Janssen DJ, de Hosson SM, bij de Vaate E, Mooren KJ, Baas AA. Attitudes toward opioids for refractory dyspnea in COPD among Dutch chest physicians. *Chron Respir Dis*. 2015;12(2):85–92.
24. Ekström M, Nilsson F, Abernethy AA, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease: a systematic review. *Ann Am Thorac Soc*. 2015;12(7):1079–1092.
25. Rocker G, Horton R, Currow D, Goodridge D, Young J, Booth S. Palliation of dyspnoea in advanced COPD: revisiting a role for opioids. *Thorax*. 2009;64(10):910–915.
26. Currow DC, Quinn S, Greene A, Bull J, Johnson MJ, Abernethy AP. The longitudinal pattern of response when morphine is used to treat chronic refractory dyspnea. *J Palliat Med*. 2013;16(8):881–886.
27. Rocker GM, Simpson AC, Joanne Young B, et al. Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *CMAJ Open*. 2013;1(1):E27–E36.
28. Johnson MJ, Abernethy AP, Currow DC. Gaps in the evidence base of opioids for refractory breathlessness. A future work plan? *J Pain Symptom Manage*. 2012;43(3):614–624.
29. Mularski RA, Campbell ML, Asch SM, et al. A review of quality of care evaluation for the palliation of dyspnea. *Am J Respir Crit Care Med*. 2010;181(6):534–538.
30. Ekström M, Bornefalk-Hermansson A, Abernethy A, Currow D. Low-dose opioids should be considered for symptom relief also in advanced chronic obstructive pulmonary disease (COPD). *Evid Based Med*. 2015;20(1):39.
31. Ekström MP, Abernethy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. *BMJ*. 2015;349:g7617.

Paper III

Cochrane Library

Cochrane Database of Systematic Reviews

Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy (Review)

Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D

Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D.
Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy.
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD006429.
DOI: 10.1002/14651858.CD006429.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy

Magnus Ekström[1], Zainab Ahmadi[1], Anna Bornefalk-Hermansson[2], Amy Abernethy[3], David Currow[4]

[1]Department of Clinical Sciences, Division of Respiratory Medicine & Allergology, Lund University, Lund, Sweden. [2]Department of Statistics, Uppsala University, Uppsala, Sweden. [3]CLHC, Duke University Medical Center, Durham, North Carolina, USA. [4]Department of Palliative and Supportive Services, Flinders University, Daw Park, Australia

Contact address: Magnus Ekström, Department of Clinical Sciences, Division of Respiratory Medicine & Allergology, Lund University, Lund, Sweden. pmekstrom@gmail.com.

Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 11, 2016.
Review content assessed as up-to-date: 12 July 2016.

Citation: Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD006429. DOI: 10.1002/14651858.CD006429.pub3.

ABSTRACT

Background

Breathlessness is a cardinal symptom of chronic obstructive pulmonary disease (COPD). Long-term oxygen therapy (LTOT) is given to improve survival time in people with COPD and severe chronic hypoxaemia at rest. The efficacy of oxygen therapy for breathlessness and health-related quality of life (HRQOL) in people with COPD and mild or no hypoxaemia who do not meet the criteria for LTOT has not been established.

Objectives

To determine the efficacy of oxygen versus air in mildly hypoxaemic or non-hypoxaemic patients with COPD in terms of (1) breathlessness; (2) HRQOL; (3) patient preference whether to continue therapy; and (4) oxygen-related adverse events.

Search methods

We searched the Cochrane Airways Group Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase, to 12 July 2016, for randomised controlled trials (RCTs). We handsearched the reference lists of included articles.

Selection criteria

We included RCTs of the effects of non-invasive oxygen versus air on breathlessness, HRQOL or patient preference to continue therapy among people with COPD and mild or no hypoxaemia (partial pressure of oxygen (PaO_2) > 7.3 kPa) who were not already receiving LTOT. Two review authors independently assessed articles for inclusion in the review.

Data collection and analysis

Two review authors independently collected and analysed data. We assessed risk of bias by using the Cochrane 'Risk of bias tool'. We pooled effects recorded on different scales as standardised mean differences (SMDs) with 95% confidence intervals (CIs) using random-effects models. Lower SMDs indicated decreased breathlessness and reduced HRQOL. We performed subanalyses and sensitivity analyses and assessed the quality of evidence according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Main results

Compared with the previous review, which was published in 2011, we included 14 additional studies (493 participants), excluded one study and included data for meta-analysis of HRQOL. In total, we included in this review 44 studies including 1195 participants, and we included 33 of these (901 participants)in the meta-analysis.

We found that breathlessness during exercise or daily activities was reduced by oxygen compared with air (32 studies; 865 participants; SMD -0.34, 95% CI -0.48 to -0.21; I^2 = 37%; low-quality evidence). This translates to a decrease in breathlessness of about 0.7 points on a 0 to 10 numerical rating scale. In contrast, we found no effect of short-burst oxygen given before exercise (four studies; 90 participants; SMD 0.01, 95% CI -0.26 to 0.28; I^2 = 0%; low-quality evidence). Oxygen reduced breathlessness measured during exercise tests (25 studies; 442 participants; SMD -0.34, 95% CI -0.46 to -0.22; I^2 = 29%; moderate-quality evidence), whereas evidence of an effect on breathlessness measured in daily life was limited (two studies; 274 participants; SMD -0.13, 95% CI, -0.37 to 0.11; I^2 = 0%; low-quality evidence).

Oxygen did not clearly affect HRQOL (five studies; 267 participants; SMD 0.10, 95% CI -0.06 to 0.26; I^2 = 0%; low-quality evidence). Patient preference and adverse events could not be analysed owing to insufficient data.

Authors' conclusions

We are moderately confident that oxygen can relieve breathlessness when given during exercise to mildly hypoxaemic and non-hypoxaemic people with chronic obstructive pulmonary disease who would not otherwise qualify for home oxygen therapy. Most evidence pertains to acute effects during exercise tests, and no evidence indicates that oxygen decreases breathlessness in the daily life setting. Findings show that oxygen does not affect health-related quality of life.

PLAIN LANGUAGE SUMMARY

Oxygen therapy for breathless people with chronic obstructive pulmonary disease with only mildly or moderately decreased oxygen in the blood

Review question

We reviewed the evidence regarding effects of oxygen compared with air on breathlessness in people with chronic obstructive pulmonary disease (COPD) with only mildly or moderately decreased blood oxygen levels.

Background

People with COPD are sometimes prescribed oxygen therapy to reduce the severity of breathlessness. However, the use of oxygen in people who do not have severely reduced levels of oxygen in their bloodstream remains controversial, as little is known about its effectiveness. Additionally, oxygen is relatively costly and is not given without risk, particularly to smokers because of the risk of fire.

Study characteristics

We examined the research published to 12 July 2016. We included studies of oxygen therapy versus air delivered through nasal prongs or mask during exertion, continuously, 'as needed' over a defined period or as short-burst oxygen before exertion. Study participants were 18 years of age or older, had received a diagnosis of COPD, had low oxygen levels in the blood and did not receive long-term oxygen therapy. We included a total of 44 studies (1195 participants) in this review. Compared with the previous review, which was published in 2011, we have added 14 studies (493 participants) to this review.

Key results

We found that oxygen can modestly reduce breathlessness. To be effective, oxygen has to be given during exercise. Most studies evaluated oxygen given during exercise testing in the laboratory. Oxygen therapy during daily life had uncertain effects on breathlessness and did not clearly change patient quality of life.

Quality of the evidence

We rated the quality of evidence using one of the following grades: very low, low, moderate or high. For very low-quality evidence, we were uncertain about the results. With high-quality evidence, we were very certain about the results. We found that evidence for oxygen given for breathlessness was moderate to low. We are moderately confident that oxygen can relieve breathlessness when given

during exercise to people with COPD with mildly or moderately decreased blood oxygen levels. However, most studies reported acute effects during an exercise test, and no evidence suggests that oxygen decreases breathlessness during daily life. Findings indicate that oxygen does not affect health-related quality of life.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy

Patient or population: patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy
Intervention: oxygen delivered through a non-invasive method
Comparison: air delivered through the same non-invasive method

Outcomes	Difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Breathlessness - all trials Lower score indicates improvement in breathlessness	**SMD 0.31, SD lower** (0.43 lower to 0.2 lower)	865 (32)	⊕⊕◯◯ Low[a]	This corresponds to 0.65 points lower (0.90 lower to 0.42 lower) on a 0-10 NRS.*
Breathlessness - subgroup analysis - studies using short-burst oxygen Lower score indicates improvement in breathlessness	**SMD 0.03, SD lower** (0.28 lower to 0.22 higher)	90 (4)	⊕⊕◯◯ Low[b]	This corresponds to 0.06 points lower (0.59 lower to 0.46 higher) on a 0-10 NRS.*
Breathlessness - subgroup analysis - studies not using short-burst oxygen Lower score indicates improvement in breathlessness	**SMD 0.36, SD lower** (0.48 lower to 0.24 lower)	775 (28)	⊕⊕◯◯ Low[a]	This corresponds to 0.76 points lower (1.01 lower to 0.50 lower) on a 0-10 NRS.*
Breathlessness - subgroup analysis - studies measuring during exercise test Lower score indicates improvement in breathlessness	**SMD 0.34, SD lower** (0.46 lower to 0.22 lower)	591 (30)	⊕⊕⊕◯ Moderate[c]	This corresponds to 0.71 points lower (0.97 lower to 0.46 lower) on a 0-10 NRS.*
Breathlessness - subgroup analysis - studies not measuring during exercise test Lower score indicates improvement in breathlessness	**SMD 0.13, SD lower** (0.37 lower to 0.11 higher)	274 (2)	⊕⊕◯◯ Low[b]	This corresponds to 0.27 points lower (0.78 lower to 0.23 higher) on a 0-10 NRS.*

Health-related quality of life - all trials Higher scores indicate improved health-related quality of life	**SMD 0.12, SD higher** (0.04 lower to 0.28 higher)	267 (5)	⊕⊕◯◯ Low[b]	This corresponds to 0.25 points higher (0.09 lower to 0.59 higher) on a 0-10 NRS.*

*Difference on a 0-10 NRS calculated using the SD of 2.1 for the COPD group in Abernethy 2010 for individual participant data.
CI: confidence interval; OR: odds ratio; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Although the effect was consistent in exercise tests in the laboratory setting, evidence of an effect was limited for domiciliary oxygen in daily life.
[b] Few studies.
[c] Graded as moderate, as most evidence pertained to breathlessness during exercise tests.

BACKGROUND

Description of the condition

Breathlessness, a cardinal symptom of chronic obstructive pulmonary disease (COPD), is distressing to both patients and caregivers. Breathlessness is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (Parshall 2012). Breathlessness is multi-factorial (Laviolette 2014) and arises as a combination of underlying pathologies involving neural pathways and subjective central perception (Parshall 2012).

Description of the intervention

Treatment of patients with breathlessness includes management of the underlying cause(s). However, breathlessness often persists despite optimal management of underlying disease(s), that is, chronic breathlessness. Pharmacological treatment with the strongest evidence base for relieving breathlessness consists of low-dose opioids (Ekstrom 2015a). People with insufficiently relieved breathlessness are then left to try any of a number of interventions for which evidence is limited, such as supplemental oxygen therapy.

Supplemental oxygen therapy most often is administered through nasal prongs or a mask and may be prescribed continuously, during exercise or as a short burst before exercise (Hardinge 2015). Oxygen sources include oxygen concentrators (which concentrate oxygen from ambient air), cylinders of compressed oxygen and flasks of liquid oxygen. Equipment can be stationary in the home and/or portable (Hardinge 2015).

Long-term oxygen therapy (LTOT) refers to oxygen given for 15 or more hours per day to prolong survival time in people with COPD and chronic severe resting hypoxaemia (partial pressure of oxygen (PaO_2) < 7.4 kPa) or moderate hypoxaemia (PaO_2 7.4 to 7.8 kPa), together with signs of right-sided heart failure or secondary polycythemia (Cranston 2005; MRCWP 1981; NOTTG 1980). Studies in severe hypoxaemia have not evaluated whether LTOT relieves breathlessness or improves health-related quality of life (HRQOL) (Cranston 2008).

Palliative oxygen therapy refers to supplemental oxygen given to relieve symptoms in people with COPD who have no to moderate

hypoxaemia.

How the intervention might work

Oxygen given before or during physical activity might increase oxygen content of and oxygen delivery to exercising muscles. This might prolong aerobic metabolism during exertion and may decrease muscle fatigue and formation of lactic acid (O'Donnell 2001), which could lead to a decreased level of ventilatory drive and increased ventilatory capacity at a given work rate, thereby decreasing the mismatch between ventilatory drive and work and perceived severity of breathlessness (O'Donnell 2001; Parshall 2012).

Why it is important to do this review

A Cochrane review of the efficacy of palliative oxygen for breathlessness was published in 2011 (Uronis 2011; Uronis 2015). A meta-analysis of 18 trials (431 participants) reported that supplemental oxygen during exercise and activities reduced breathlessness to a greater extent than air. Short-burst oxygen before exercise did not decrease breathlessness. Review authors could not analyse HRQOL because data were insufficient. Most evidence pertained to exercise testing performed in the laboratory setting (Uronis 2011; Uronis 2015). A subsequent Cochrane review of four studies (331 participants) suggested that longer-term treatment with ambulatory oxygen relieves breathlessness more effectively than air after exercise in people with COPD (Ameer 2014). Current guidelines do not recommend palliative oxygen therapy in COPD, as evidence on treatment in the domiciliary and daily life setting remains insufficient (Ekstrom 2015b; Hardinge 2015). Despite this, palliative oxygen therapy might be commonly prescribed in clinical practice (Abernethy 2005; Stringer 2004).

The discrepancy between current clinical practice and available evidence has important implications. First, patients may be prescribed ineffective treatment. Second, oxygen therapy is not a benign intervention. Functional restriction caused by tubing, concentrators or cylinders and the "sick role" may limit quality of life. People also express concern about being reliant on a machine. Nasal cannulae can lead to nasal irritation and can increase the risk of nosebleeds. Oxygen therapy carries a fire risk, particularly for smokers (Robb 2003). Serious burn injuries seem infrequent in LTOT with strict adherence to eligibility criteria and contraindications, including smoking cessation (Tanash 2015). A small but increased risk of exacerbated hypercarbia is possible, and home oxygen therapy is relatively expensive. If patients do not meet the criteria for LTOT, they may have to pay for oxygen therapy themselves or may receive it on compassionate use grounds (Guyatt 2000). Improved evidence regarding optimal use of palliative oxygen therapy is needed.

Since the previous Cochrane reviews were published (Uronis 2011; Uronis 2015), several studies of palliative oxygen therapy have been reported, including some larger trials (Abernethy 2010 and Moore 2011).

This is an update of the Cochrane review published in 2011 (Uronis 2011; Uronis 2015).

OBJECTIVES

To determine the efficacy of oxygen versus air in mildly hypoxaemic or non-hypoxaemic patients with COPD in terms of (1) breathlessness; (2) HRQOL; (3) patient preference whether to continue therapy; and (4) oxygen-related adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included studies with participants 18 years of age or older who had COPD, had mild or no hypoxaemia (mean PaO_2 > 7.3 kPa) and did not receive LTOT. For studies that also included participants without COPD, we obtained from study authors individual participant data for those with COPD and included only these data in the analyses.

Types of interventions

We included studies of oxygen therapy versus air delivered by a non-invasive method at any inspired dose above that of ambient air (> 21%). Oxygen/air should have been delivered during exertion, continuously or 'as needed' over a defined period, or as short-burst oxygen before exertion. Short-burst oxygen was defined as therapy given during a short, defined period just before exertion. We did not include short-burst oxygen given only after exertion.

Types of outcome measures

Primary outcomes

1. Level of breathlessness measured on any validated scale

Secondary outcomes

1. HRQOL measured on any validated scale
2. Blinded participant preference to continue therapy
3. Adverse events

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of multiple bibliographic databases and from handsearching of respiratory journals and meeting abstracts (see Appendix 1 for details). We conducted additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 6), MEDLINE (to 12 July 2016) and Embase (to 12 July 2016). Search strategies are shown in Appendix 2; Appendix 3; Appendix 4; and Appendix 5. We also searched ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) for ongoing trials by using appropriately adapted search terms. We searched all databases from their inception to 12 July 2016, with no restriction on language of publication.

Searching other resources

We handsearched relevant review articles and reference lists of identified articles.

Data collection and analysis

Selection of studies

Two review authors (ME and ZA) independently selected studies that fulfilled all inclusion criteria.

1. RCT.
2. Included participants 18 years of age or older.
3. At least one participant with COPD.
4. Mean PaO_2 > 7.3 kPa at baseline.
5. Only participants not already receiving LTOT.
6. Comparison of oxygen versus air at any dose delivered through a non-invasive method.
7. Endpoint of breathlessness or HRQOL.

Data extraction and management

Two review authors (ME and ZA) independently extracted data and resolved disagreements by consensus and discussion with a third review author (DC), if needed. We contacted the authors of primary studies to obtain additional information when necessary.

Assessment of risk of bias in included studies

Two review authors (ME and ZA) independently assessed each study for risk of bias in terms of allocation sequence generation, allocation concealment, blinding of participants and outcome assessors, handling of missing data, selective outcome reporting and other threats to the validity of studies, in line with recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We conducted a retrospective risk of bias assessment using the above method applied to all studies from the review published in 2011 (Uronis 2011).

Measures of treatment effect

We performed meta-analyses as appropriate and possible, given available data. We analysed outcomes on different scales as standardised mean differences (SMDs) using random-effects models. We compared within-patient effects from both periods of cross-over trials. Meta-analyses included post scores only. For studies for which post scores were not available, we reported changes from baseline scores separately. For breathlessness during exercise, we used scores measured at a similar time point in both groups (iso-scores) when available. For studies evaluating different oxygen doses, we included only the lowest dose in the analysis. We reversed St George's Respiratory Quotient (SGRQ) scores (as increasing scores indicate worse quality of life), so that higher scores on all HRQOL measures indicated better quality of life in all analyses.

Unit of analysis issues

We estimated standard errors for paired outcome data from cross-over trials, according to Follmann 1992. We estimated correlations between repeated outcomes from P values when available, and for studies for which little evidence was available to impute a correlation coefficient from another trial, we assumed a value of 0.5 (Follmann 1992). We performed sensitivity analyses using different imputed correlations.

Dealing with missing data

When statistics essential for analysis were missing (e.g. group means and standard deviations for both groups were not reported) and could not be calculated from other data, we attempted to contact study authors to obtain the missing data. We assumed that loss of participants that occurred before baseline measurements were taken had no effect on eventual outcome data provided by the study. We assessed any losses that occurred after baseline measurements had been taken and discussed them on an intention-to-treat basis.

Assessment of heterogeneity

We assessed statistical heterogeneity by using the I^2 statistic and by inspecting funnel plots.

Assessment of reporting biases

We assessed possible publication bias by using funnel plots.

Data synthesis

We performed meta-analyses by using Review Manager software version 5.3 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We conducted the following a priori subgroup analyses on the presence/absence of:

1. short-burst oxygen therapy;
2. exertional desaturation (oxygen saturation (SaO_2) < 88% as entry criteria, or mean PaO_2 < 8 kPa on exertion);
3. baseline mean PaO_2 breathing air < 9.3 kPa;
4. measurement during exertion;
5. laboratory setting (compared with domiciliary setting);
6. measured acute oxygen effect (test on oxygen vs air) compared with long-term oxygen effect (test on the same inhaled gas after a period of oxygen or air); and
7. mean oxygen dose > 2 L/min. For studies that reported only administered fraction of inspired oxygen (FiO_2), an oxygen dose > 2 L/min was defined as FiO_2 > 0.27.

Sensitivity analysis

We conducted the following a priori sensitivity analyses by excluding studies with:

1. measurement at peak exertion (compared with iso-time);
2. high risk of bias for any bias category;
3. any participant without COPD; and
4. outlier findings (based on forest and funnel plots).

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Participant characteristics

All 1195 participants included in the analysis had COPD (Table 1). Baseline PaO_2 was provided in 30 of 44 studies, ranging from 7.7 to 11.3 kPa. Twelve of the remaining studies provided baseline oxygen saturation ranging from 90% to 97% (Table 1).

Twenty studies reported mean baseline breathlessness at rest as follows: visual analogue score (VAS) score 5 to 40 mm (100 mm VAS); Borg score 0.1 to 1 point (Table 1).

Intervention characteristics

All studies compared oxygen versus air, delivered via the same non-invasive method in both groups. The most frequent mode of administration was the nasal cannula (22 studies) (Abernethy 2010; Davidson 1988; Dyer 2012; Eaton 2002; Eaton 2006; Haidl 2004; Jolly 2001a; Jolly 2001b; Knebel 2000; Kurihara 1989; Lewis 2003; McDonald 1995; McKeon 1988a; McKeon 1988b; Moore 2011; Nonoyama 2007; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Spielmanns 2014; Wadell 2001; Woodcock 1981) followed by mouthpiece/valve (13 studies) (Bruni 2012a; Bruni 2012b; Dean 1992; Emtner 2003a; Emtner 2003b; Eves 2006; Laude 2006; Maltais 2001; Moore 2009; O'Donnell 1997; Scorsone 2010; Somfay 2001; Swinburn 1984) and mask (eight studies) (Killen 2000; Leach 1992; Miki 2012: Nandi 2003; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Voduc 2010) or unknown (one study) (Ishimine 1995).

Doses of oxygen provided ranged from 2 to 6 L/min via nasal cannula, and FiO_2 ranged from 24% to 75% via mask/mouthpiece (Table 1).

A total of 32 studies (Bruni 2012a; Bruni 2012b; Davidson 1988; Dean 1992; Eaton 2006; Emtner 2003a; Emtner 2003b; Eves 2006; Haidl 2004; Ishimine 1995; Jolly 2001a; Jolly 2001b; Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Leach 1992; Maltais 2001; McKeon 1988b; Miki 2012; O'Donnell 1997; Oliveira 2012a; Oliveira 2012b; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Spielmanns 2014; Swinburn 1984; Voduc 2010; Wadell 2001; Woodcock 1981) provided continuous oxygen during exercise testing - six-minute walk test (6MWT), endurance shuttle walk test, incremental shuttle walk test, step test or cycle exercise test. .

Six studies (Abernethy 2010; Eaton 2002; McDonald 1995; Moore 2011; Nonoyama 2007; Ringbaek 2013) provided domiciliary oxygen during daily life and activities.

Four studies (Killen 2000; Lewis 2003; McKeon 1988a; Nandi 2003) gave participants short-burst oxygen therapy before exertion.

Outcome characteristics

Breathlessness

Twenty-nine studies (Bruni 2012a; Bruni 2012b; Dean 1992; Eaton 2002; Emtner 2003a; Emtner 2003b; Eves 2006; Haidl 2004; Jolly 2001a; Jolly 2001b; Kurihara 1989; Laude 2006; Lewis 2003; Maltais 2001; McDonald 1995; Miki 2012; Moore 2009; Nonoyama 2007; O'Donnell 1997; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Voduc 2010; Wadell 2001) measured breathlessness using a modified Borg scale, nine studies (Davidson 1988; Killen 2000; Knebel 2000; Leach 1992; McKeon 1988a; McKeon 1988b; Nandi 2003;

Swinburn 1984; Woodcock 1981) used a VAS and five studies (Abernethy 2010; Dyer 2012; Eaton 2006; Ishimine 1995; Moore 2011) used other scales (Table 1).

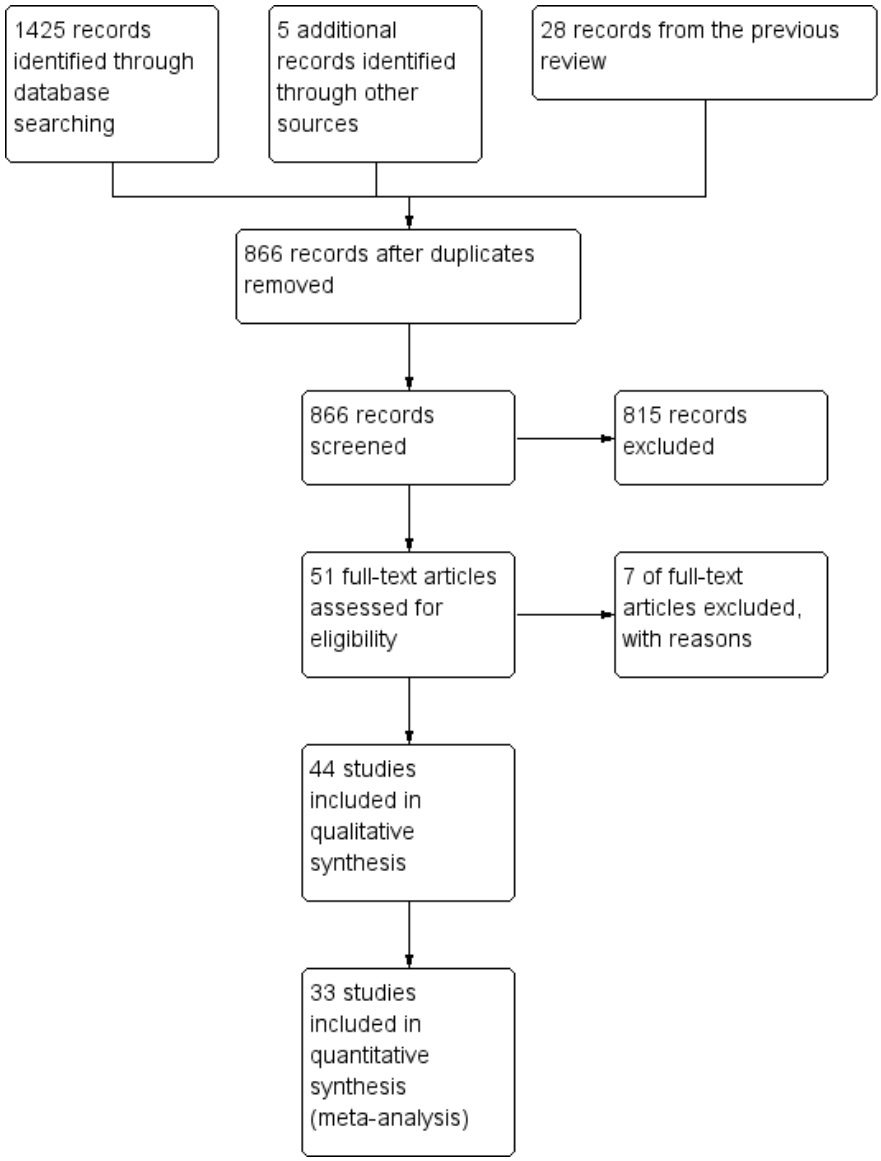
HRQOL

Seven studies (Eaton 2002; Eaton 2006; Emtner 2003a; Emtner 2003b; Moore 2011; Rooyackers 1997a; Rooyackers 1997b) measured HRQOL as Chronic Respiratory Questionnaire (CRQ) total score, 10 studies (Dyer 2012; Eaton 2002; Eaton 2006; Emtner 2003a; Emtner 2003b; McDonald 1995; Moore 2011; Nonoyama 2007; Rooyackers 1997a; Rooyackers 1997b) as CRQ subdomains, five studies (Eaton 2002; Eaton 2006; Emtner 2003a; Emtner 2003b; Spielmanns 2014) as Short Form-36 (SF-36) total score and two studies (Nonoyama 2007; Ringbaek 2013) as SGRQ total score. One study (Abernethy 2010) measured perceived overall well-being on a 0 to 10 VAS and HRQOL over weeks or months (Table 1), with higher scores indicating better HRQOL.

Results of the search

Of an identified 866 unique records, we included 44 studies (1195 participants) in this update review (Figure 1). Compared with the previous review, which was published in 2011 (Uronis 2011), we included 14 additional studies (Abernethy 2010; Bruni 2012a; Bruni 2012b; Dyer 2012; Miki 2012; Moore 2011; Nonoyama 2007; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Ringbaek 2013; Scorsone 2010; Spielmanns 2014; Voduc 2010), and we excluded one additional trial (Garrod 2000).

Figure 1. Study flow diagram.



Included studies

We have provided characteristics of the 44 included studies in the Characteristics of included studies table and in Table 1. Of 44 included studies, 31 were cross-over trials (Bruni 2012a; Bruni 2012b; Davidson 1988; Dean 1992; Eaton 2002; Eves 2006; Ishimine 1995; Jolly 2001a; Jolly 2001b; Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Leach 1992; Lewis 2003; Maltais 2001; McDonald 1995; McKeon 1988a; McKeon 1988b; Miki 2012; Moore 2009; Nandi 2003; Nonoyama 2007; O'Donnell 1997; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Somfay 2001; Swinburn 1984; Voduc 2010; Woodcock 1981) and 13 were parallel-group trials (Abernethy 2010; Dyer 2012; Eaton 2006; Emtner 2003a; Emtner 2003b; Haidl 2004; Moore 2011; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Spielmanns 2014; Wadell 2001).

Ten studies (Bruni 2012a; Bruni 2012b; Emtner 2003a; Emtner 2003b; Jolly 2001a; Jolly 2001b; Oliveira 2012a; Oliveira 2012b; Rooyackers 1997a; Rooyackers 1997b) included two different comparisons of independent groups, which we included in the analysis.

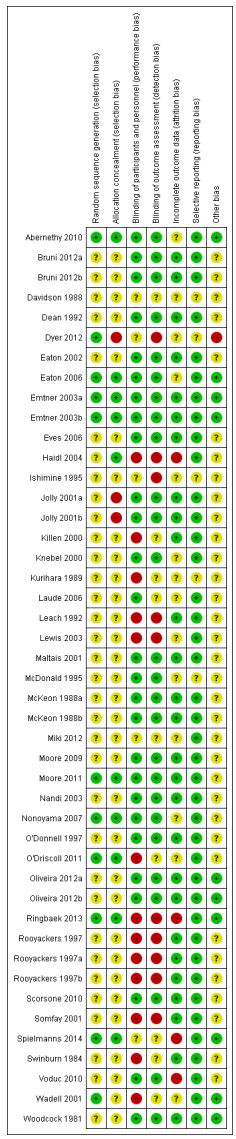
Excluded studies

We have presented excluded trials with reasons for exclusion in the Characteristics of excluded studies table. We identified two ongoing or recently completed trials but did not include them in this review, as data were unavailable: the Long-Term Oxygen Therapy Trial (LOTT; registered at ClinicalTrials.gov: NCT00692198) of supplemental oxygen in 738 participants with COPD and moderate hypoxaemia at rest and/or exertion, which included measures of breathlessness and HRQOL; and another recently completed cross-over study comparing effects of supplemental oxygen versus air on breathlessness during exercise testing in 11 participants with COPD, which was presented as an abstract (Vesteng 2015).

Risk of bias in included studies

We have provided risk of bias judgements for each study at the end of each Characteristics of included studies table and have summarised each risk of bias category in Figure 2. Methods were poorly reported in most of the included studies. We assessed risk of bias as mostly unclear regarding selection bias, but as low for more than half of studies regarding performance, detection, attrition and reporting bias, and as mostly unclear regarding other biases (Figure 2).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Although all studies were described as randomised, we could verify that sequence generation was adequate in only 11 studies (Abernethy 2010; Dyer 2012; Eaton 2006; Emtner 2003a; Emtner 2003b; Moore 2011; Nonoyama 2007; O'Driscoll 2011; Ringbaek 2013; Spielmanns 2014; Wadell 2001). Concealment of allocation was adequate in 10 studies and inadequate in three studies (Figure 2). For remaining studies, we had insufficient information to determine risk of bias for allocation procedures.

Blinding

Masking of treatment was undertaken in several studies. For five studies, we were unable to determine how blinding of study participants or investigators had been achieved. For 12 studies (Haidl 2004; Killen 2000; Kurihara 1989; Leach 1992; Lewis 2003; O'Driscoll 2011; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Somfay 2001; Swinburn 1984; Wadell 2001), we found that blinding was not undertaken, or investigators knew which containers contained oxygen. The remaining 27 studies attempted blinding of both study participants and study investigators (Figure 2).

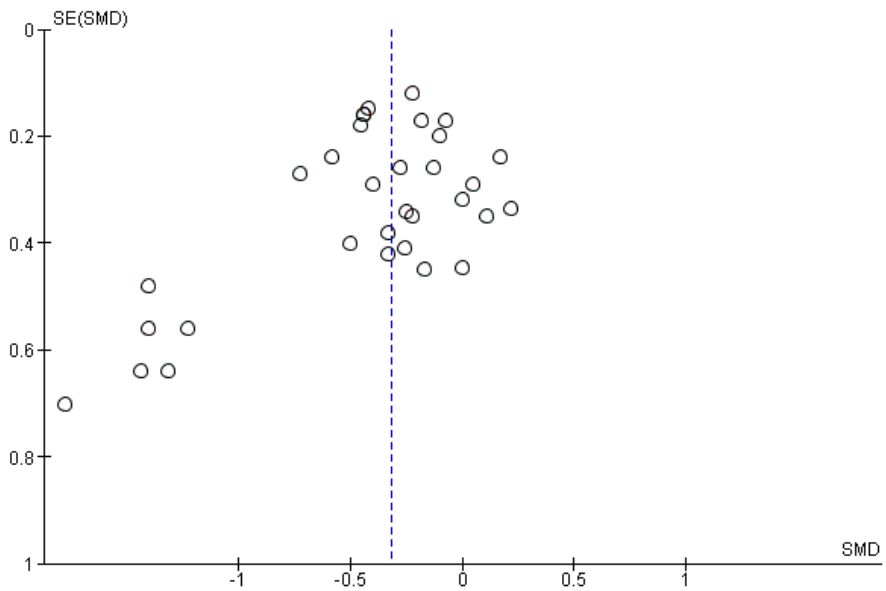
Incomplete outcome data

Twenty-six studies (Bruni 2012a; Bruni 2012b; Dean 1992; Eaton 2002; Emtner 2003a; Emtner 2003b; Eves 2006; Jolly 2001a; Jolly 2001b; Killen 2000; Leach 1992; Maltais 2001; McKeon 1988a; McKeon 1988b; Moore 2009; Moore 2011; Nandi 2003; O'Donnell 1997; Oliveira 2012a; Oliveira 2012b; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Swinburn 1984; Woodcock 1981) reported no withdrawals. Cross-over studies analyse within-participant differences; therefore, participants who did not complete both treatment periods were not included in the analyses. For the remaining studies, we could not reliably ascertain how missing data were handled (Figure 2).

Selective reporting

Possible publication bias on the effect of oxygen on breathlessness was indicated by the funnel plot shown in Figure 3. Studies showing a larger positive effect of oxygen on breathlessness were more likely to have lower precision. Asymmetry was apparent, with few studies with low precision reporting no or non-beneficial effects of oxygen on breathlessness (Figure 3).

Figure 3. Funnel plot of comparison: 1 Oxygen versus air, outcome: 1.1 Breathlessness - all trials.



Other potential sources of bias

We categorised the risk of other sources of bias as high for Dyer 2012 and as unclear for most studies.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table

All comparisons consisted of oxygen versus air delivered by the same mechanism among participants with COPD and no or mild hypoxaemia.

Primary outcome: breathlessness

The meta-analysis of breathlessness included 32 studies with 865 participants (Abernethy 2010; Bruni 2012a; Bruni 2012b; Davidson 1988; Dean 1992; Eaton 2002; Emtner 2003a; Emtner 2003b; Eves 2006; Jolly 2001a; Jolly 2001b; Killen 2000; Knebel 2000; Kurihara 1989; Laude 2006; Lewis 2003; McDonald 1995; McKeon 1988a; Miki 2012; Moore 2011; Nandi 2003; Nonoyama 2007; O'Donnell 1997; Oliveira 2012a; Oliveira 2012b; Ringbaek 2013; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Voduc 2010; Woodcock 1981).

In pooled analysis of all trials, we found that oxygen reduced breathlessness (SMD -0.31, 95% CI -0.43 to -0.20; I^2 = 29%; Analysis 1.1; low-quality evidence).

A priori subgroup analyses of breathlessness

Short-burst oxygen therapy

Short-burst oxygen therapy before exertion did not reduce breathlessness (SMD -0.03, 95% CI -0.28 to 0.22; four studies; I^2 = 0%), whereas oxygen given during exercise or daily activities did reduce breathlessness (SMD -0.36, 95% CI -0.48 to -0.24; 28 studies; I^2 = 27%; Analysis 1.2; low-quality evidence). Differences between groups were statistically significant (P = 0.02).

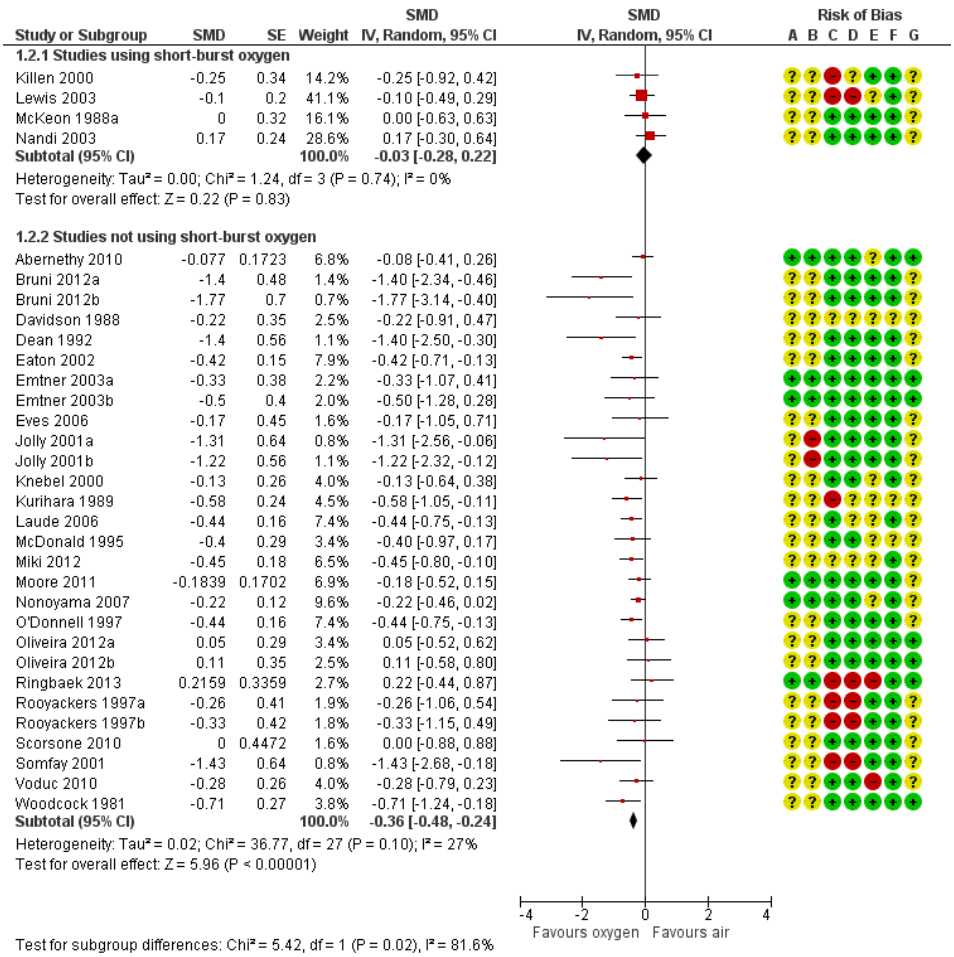
Exertional desaturation

In studies with desaturation during exercise, defined as SaO_2 < 88% among entry criteria or mean PaO_2 < 8 kPa on exertion, oxygen reduced breathlessness (SMD -0.28, 95% CI -0.39 to -0.16; 16 studies), but the effect tended to be greater in studies without exertional desaturation (SMD -0.47, 95% CI -0.69 to -0.24; 15 studies; Analysis 1.3). P = 0.14 for differences between groups.

Baseline mean PaO_2 (air) < 9.3 kPa

The effect of oxygen was similar among studies with baseline mean PaO_2 (air) < 9.3 kPa (SMD -0.28, 95% CI -0.48 to -0.07; seven studies) and studies with PaO_2 (air) $\geq$ 9.3 kPa (SMD -0.33, 95% CI -0.47 to -0.20; 25 studies; Analysis 1.4), as shown in Figure 4. P = 0.65 for differences between groups.

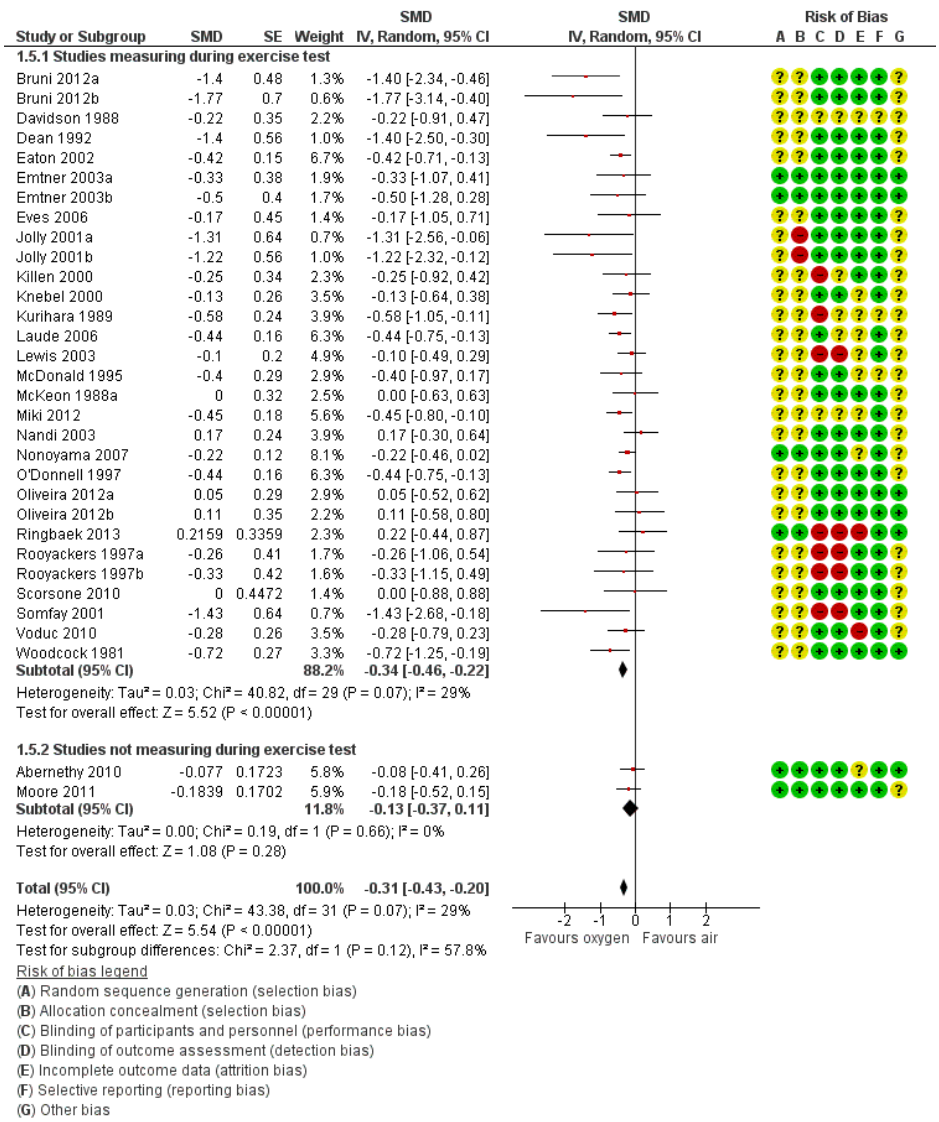
Figure 4. Forest plot of comparison: 1 Oxygen versus air, outcome: 1.2 Breathlessness - subgroup analysis - short-burst oxygen versus not.



Measurement during exercise test

Most studies measured breathlessness during exertion (SMD -0.34, 95% CI -0.46 to -0.22; 30 studies); only two studies measured breathlessness in daily life and found a smaller and less precise effect of oxygen (SMD -0.13, 95% CI -0.37 to 0.11; two studies; Analysis 1.5; moderate-quality evidence), as shown in Figure 5. P = 0.12 for differences between groups.

Figure 5. Forest plot of comparison: 1 Oxygen versus air, outcome: 1.5 Breathlessness - subgroup analysis - measured during exercise test versus not.



Laboratory setting

Most studies measured breathlessness during exercise testing in a laboratory setting (SMD -0.37, 95% CI -0.52 to -0.22; 25 studies). The effect of oxygen was less in non-laboratory domiciliary settings (SMD -0.23, 95% CI -0.36 to -0.09; seven studies; Analysis 1.6). P = 0.16 for differences between groups.

Short-term versus long-term (training) oxygen effects

Most studies evaluated acute effects of oxygen by comparing an exercise test on oxygen versus an exercise test on air (SMD -0.34, 95% CI -0.46 to -0.22; 29 studies). Investigators evaluated a potential longer-term (training) effect of oxygen by performing a test on the same gas after a (training) period with oxygen or air. Only three studies performed this evaluation and found no evidence of a long-term effect of oxygen (SMD -0.09, 95% CI -0.37 to 0.19; three studies; Analysis 1.7). P = 0.11 for differences between groups.

Mean oxygen dose > 2 L/min

Most studies evaluated oxygen at a dose > 2 L/min, which tended to reduce breathlessness more (SMD -0.35, 95% CI -0.49 to -0.21; 25 studies) than an oxygen dose $\leq$ 2 L/min (SMD -0.19, 95% CI -0.39 to 0.01; five studies; Analysis 1.8). P = 0.19 for differences between groups.

A priori sensitivity analyses of breathlessness

Analysis excluding trials measuring breathlessness at peak exertion

Oxygen reduced breathlessness measured at iso-time (SMD -0.37, 95% CI -0.50 to -0.24; 26 studies; I^2 = 32%) but had no effect on breathlessness measured at peak exertion (SMD -0.14, 95% CI -0.33 to 0.05; six studies; I^2 = 0%; Analysis 1.9).

Analysis excluding trials with high risk of bias

When we excluded trials with high risk of bias for any bias category (risk of bias shown in Figure 2), the effect of oxygen on breathlessness remained unchanged (SMD -0.30, 95% CI -0.41 to -0.20; 25 studies; I^2 = 14%; Analysis 1.10).

Analysis excluding trials with any participant without COPD

All participants included in the meta-analysis had COPD. For studies that included non-COPD participants, we used individual participant data for the COPD subgroup (Abernethy 2010).

Analysis excluding outlier findings

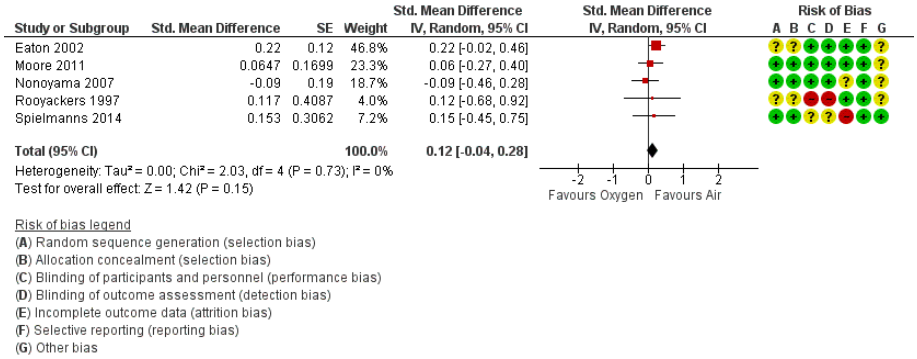
Upon inspecting forest and funnel plots (Figure 3; Figure 4), we identified five outlier findings (Bruni 2012a; Bruni 2012b; Dean 1992; Jolly 2001a; Jolly 2001b; Somfay 2001). Exclusion of the outliers revealed that oxygen reduced breathlessness, but the effect became slightly smaller (SMD -0.27, 95% CI -0.35 to -0.18; 26 studies; I^2 = 0%; Analysis 1.11). The effect of continuous oxygen during exertion or daily activities (no short-burst therapy) was similar after outliers were excluded (SMD -0.30, 95% CI -0.39 to -0.20; 22 studies; I^2 = 0%; Analysis 1.12).

Secondary outcome: HRQOL

Meta-analysis

Twelve studies (Abernethy 2010; Dyer 2012; Eaton 2002; Eaton 2006; Emtner 2003a; Emtner 2003b; McDonald 1995; Moore 2011; Nonoyama 2007; Ringbaek 2013; Rooyackers 1997; Spielmanns 2014) examined changes in HRQOL. Of these, we were able to include five studies (267 participants) (Eaton 2002; Moore 2011; Nonoyama 2007; Rooyackers 1997; Spielmanns 2014) in the meta-analysis. Oxygen had no clear effect on HRQOL (SMD 0.12, 95% CI -0.04 to 0.28; five studies; I^2 = 0%; Analysis 1.13; low-quality evidence), as shown in Figure 6. In the analysis, higher scores indicated better HRQOL.

Figure 6. Forest plot of comparison: 1 Oxygen versus air, outcome: 1.13 Health-related quality of life - all trials.



Descriptive analysis of studies not included in meta-analysis

We did not include seven studies in the meta-analysis, as they did not use a validated scale of HRQOL (Abernethy 2010), reported only HRQOL subdomain scores (Dyer 2012; McDonald 1995), reported change scores (Emtner 2003a; Emtner 2003b; Ringbaek 2013) or provided data that could not be combined in the analysis (Eaton 2006). For all scales used, higher scores indicated better quality of life.

Abernethy 2010 measured overall perceived quality of life over the past two days on a 0 to 10 numerical rating scale (NRS) based on a daily diary kept over seven days. In the subgroup with COPD (n = 158), improvement from baseline at day 7 was 0.8 points (standard deviation (SD) 2.0) in the oxygen group and 0.3 points (SD 1.9) in the air group.

Dyer 2012 measured change from baseline in CRQ subdomain scores after six to seven weeks of pulmonary rehabilitation using oxygen or air. The only statistically and clinically significant change was found in the CRQ mastery score. For oxygen compared with air, the mean difference was -0.1 (95% CI -0.9 to 0.7; P = 0.76) for the domain CRQ breathlessness, 0.5 (95% CI -0.2 to 1.2; P = 0.15) for CRQ emotion, 0.7 (95% CI -0.1 to 1.5; P = 0.10) for CRQ fatigue and 0.7 (95% CI 0.0 to 1.4; P = 0.006) for CRQ mastery scores.

Eaton 2006 was a randomised, controlled, parallel-group trial that included three arms as follows: oxygen, air and usual care. The only domain of the CRQ to show statistical significance (P = 0.045) was emotional function; the greatest improvement was noted in the usual care group, which received neither oxygen nor air.

For Emtner 2003a and Emtner 2003b, CRQ total score and subscores increased significantly in both groups. Only in mastery was a statistically significantly greater improvement detected in the oxygen-trained group (P < 0.05). For the Short Form-36, a significant difference (improvement) in general health was seen in the oxygen compared with the air group (P < 0.05).

McDonald 1995 measured subdomains of CRQ and noted statistically significant improvement in all CRQ subdomains for the comparison of baseline scores versus scores after six weeks of oxygen therapy (P < 0.02 for all domains). However, when scores after oxygen therapy were compared with scores after air, they reported no statistically or clinically significant differences.

Ringbaek 2013 measured total SGRQ score at 7 weeks compared with baseline. Mean changes from baseline were -1.8 (SD 8) for the oxygen group and -3.2 (SD 7.2) for no oxygen group; the difference between groups was not statistically significant (P = 0.80).

Secondary outcome: blinded patient preference

Five studies (Abernethy 2010; Eaton 2002; Killen 2000; McDonald 1995; Moore 2011) assessed patient preference to continue therapy (oxygen vs air delivered by the same mechanism) at a time when participants were still blinded. Owing to heterogeneity of the reported data, we could not perform a meta-analysis.

Abernethy 2010 assessed patient preference after seven days of blinded oxygen/air by asking the question, "Reviewing the benefits and burdens of your experience with the treatment over the past week, would you want to continue this treatment?" Among participants with COPD who answered (N = 139), preferences to continue treatment were as follows in the oxygen group: yes 50%, maybe 27% and no 23%. In the air group, preferences were yes 41%, maybe 23% and no 36%. The difference in preference between groups was not statistically significant (P = 0.25).

Eaton 2002 asked participants (N = 41) if they were interested

in clinical provision of oxygen at study completion. Among participants identified as having a short-term response to oxygen, 14 participants did not wish to be considered for continued therapy. Eleven of these 14 (76%) cited poor tolerability or acceptability as the reason.

Killen 2000 studied short-burst oxygen given immediately before and after walking up a flight of steps, asking participants which blinded gas they preferred. Of 18 participants, five preferred oxygen before ascending the stairs, three preferred air and three had no preference. The remaining seven participants preferred to receive oxygen at the top of the stairs. As a group, participants expressed no statistically significant preference for oxygen therapy (P = 0.12).

McDonald 1995 included both acute assessments and a domiciliary portion that lasted six weeks with each gas, asking participants (N = 26) at the end of the study which six-week period they preferred. Fifty percent preferred the period when they received oxygen; the remaining 50% preferred air or had no preference.

Moore 2011 asked participants whether they wanted to continue or discontinue the provision of domiciliary cylinders after the 12-week study period. Preferences were similar between groups; 35 of 65 (54%) wanted to continue in the oxygen group compared with 37 of 73 (51%) in the air group.

Secondary outcome: adverse events

Adverse events were insufficiently and inconsistently reported; therefore, meta-analysis was not possible.

Abernethy 2010 included a total of 65 participants in the oxygen group and 70 in the air group. Serious adverse events were rare, with no clinically meaningful differences between groups for moderate to extreme drowsiness (47% oxygen vs 51% air); moderate to extreme nasal irritation (29% oxygen vs 35% air); moderately to extremely troublesome nosebleeds (3% oxygen vs 3% air) and moderate to extreme anxiousness (26% oxygen vs 40% air).

Dyer 2012 included a total of 47 participants in the study. Investigators reported seven dropouts; three participants withdrew because of an exacerbation of their condition, one because of other medical problems and three for social reasons.

Eaton 2002 included a total of 41 participants in the study. Investigators reported nine dropouts; causes of dropout included morbidity for two participants and cancer for one participant in both study groups. Three in each group withdrew for personal reasons.

Eaton 2006 included a total of 25 participants in the oxygen group and 26 in the air group. Five participants in the oxygen group died, one was admitted to the hospital and three were prescribed LTOT. In the air group, two participants died, one was prescribed LTOT, one was admitted to a rest home and four were admitted to the hospital.

Emtner 2003a and Emtner 2003b included a total of 14 participants in the oxygen group and 15 in the air group. We excluded one participant from the oxygen-trained group because of illness post intervention.

Haidl 2004 included a total of 26 participants in the study. During three-year follow-up, four participants in the oxygen group died and one was given a diagnosis of cancer.

Knebel 2000 included a total of 31 participants in the study. Two participants were unable to complete all of the walks in the study because of unrelated problems (fever and migraine headache).

Laude 2006 included a total of 76 participants in the study. After randomisation, seven participants withdrew: five because of exacerbations and two for other reasons.

Lewis 2003 included a total of 18 participants in the study and reported four dropouts. Two participants failed to complete the first visit and attend the second visit (chest pain during 6MWT (n = 1), personal reasons (n = 1)). Furthermore, two participants failed to attend the second visit (clinically unstable (n = 1), other (n = 1)).

McDonald 1995 included a total of 26 participants in the study and reported seven dropouts; three participants withdrew during the first six weeks of domiciliary therapy (acute gout, muscular pain related to pulling the gas cylinder, unwillingness to continue in the study, respectively), each of whom had received cylinder air in the first six weeks. A total of four participants were withdrawn during the second six weeks: One participant died of a cerebrovascular accident and another of overwhelming pneumonia, a third was hospitalised with an acute exacerbation of COPD and the last incurred an incidental injury. All four participants had received cylinder oxygen during this second six-week trial period.

Moore 2011 included a total of 66 participants in the oxygen group and 73 in the air group. After randomisation, among those allocated to cylinder oxygen, one participant was deceased and one got unwell.

Nonoyama 2007 included a total of 27 participants in the study and reported 11 dropouts. Five were reluctant to continue, three developed resting hypoxaemia with a PaO_2 less than 55 mmHg, two died, and one was non-compliant, utilising the test mixtures for less than one hour per day.

Ringbaek 2013 included a total of 15 participants in the oxygen group and 22 in the air group. At study end (33 weeks), the mean number of adverse events did not differ significantly between treatment groups in terms of acute COPD exacerbations (P = 0.30) or number of participants with hospital admission or dropout (P = 0.59).

Spielmanns 2014 included a total of 19 participants in the oxygen group and 17 in the air group. After randomisation, in the oxygen group, five participants discontinued owing to comorbidities, and in the air group, seven discontinued because of comorbidities.

Voduc 2010 included a total of 15 participants in the study. After randomisation, three participants developed COPD exacerbations and one developed worsening of arthritis that limited exercise and thus was excluded.

Bruni 2012a; Bruni 2012b; Davidson 1988; Dean 1992; Eves 2006; Ishimine 1995; Jolly 2001a; Jolly 2001b; Killen

2000; Kurihara 1989; Leach 1992; Maltais 2001; McKeon 1988a; McKeon 1988b; Miki 2012; Moore 2009; Nandi 2003; O'Donnell 1997; O'Driscoll 2011; Oliveira 2012a; Oliveira 2012b; Rooyackers 1997a; Rooyackers 1997b; Scorsone 2010; Somfay 2001; Swinburn 1984; Wadell 2001; and Woodcock 1981 did not report adverse events.

DISCUSSION

Summary of main results

Since the previous version of this review was published in 2011 (Uronis 2011), we have included an additional 14 studies of the effects of oxygen versus air on breathlessness, we have excluded one study, and data for meta-analysis of health-related quality of life (HRQOL) are now available.

When compared with air, continuous oxygen (not short-burst oxygen) reduced breathlessness more during exercise or activity (standard mean difference (SMD) -0.36, 95% confidence interval (CI) -0.48 to -0.24), and most data pertaining to breathlessness were obtained during exercise testing in the laboratory setting. This effect translated to a mean decrease in breathlessness of 0.7 points on a 0 to 10 numerical rating scale (NRS) based on data from a recent large study (Abernethy 2010). The minimal clinically important difference in chronic breathlessness has been reported to be 1 point, with small, moderate and large effects seen at about 0.6, 1.1 and 1.8 points, respectively (Johnson 2013). It is unclear whether the effect of oxygen on breathlessness could be clinically meaningful for many participants in this setting.

Evidence for breathlessness pertains mostly to acute effects of exercise testing on breathlessness in the laboratory setting. Effects on breathlessness during daily life (not measured during an exercise test) in the domiciliary setting were smaller and were statistically non-significant (SMD -0.13, 95% CI -0.37 to 0.11).

Short-burst oxygen therapy before exertion did not affect breathlessness.

Oxygen did not clearly affect HRQOL (SMD 0.10, 95% CI -0.06 to 0.26). Blinded patient preference to continue therapy did not differ between groups given oxygen and groups given air. Investigators insufficiently reported adverse events, and we could not meta-analyse adverse event data.

Overall completeness and applicability of evidence

After an extensive database and literature search, we included 44 studies (1195 participants) in this update review. Although two relatively large studies of ambulatory oxygen have been published in recent years (Abernethy 2010; Moore 2011), additional high-quality data on effects of ambulatory oxygen in daily life, including effects on HRQOL, are needed. Good methodological rigour would include publication of a prespecified protocol outlining trial design, adequate sequence generation, randomisation, blinding (for participants and for outcome assessors) and transparent reporting of appropriate outcomes at baseline in a format suitable for meta-analysis (e.g. mean with standard deviation and sample size).

Mechanism of effect on breathlessness

The likely mechanism underpinning an effect on breathlessness is that supplemental oxygen prevents or decreases hypoxaemia during exercise, thereby reducing a hypoxaemia-related increase in ventilatory demand, dynamic hyperinflation and increased exertional breathlessness in some patients (O'Donnell 2001). This mechanism is supported by the present finding that a higher oxygen dose (> 2 L/min) was associated with a larger decrease in breathlessness. The finding that the oxygen effect was not stronger in studies of patients with exertional desaturation might reflect that the analysis was based on the study mean, and that heterogeneity in the level of exertional hypoxaemia among individual participants might have attenuated the association. Some people developed hypoxaemia during exercise despite supplemental oxygen therapy that could have increased their breathlessness scores. The issue is further complicated in that some patients might have adapted to exertional hypoxaemia, with a reduced ventilatory response to hypoxaemia and therefore less benefit of oxygen during exercise. Another hypothesis is that airflow to the face and upper airways could relieve breathlessness, possibly through increased afferent feedback mimicking increased ventilatory work (Johnson 2016; Schwartzstein 1987). This could reduce the imbalance between ventilatory demand and perceived ventilatory work and thus the level of breathlessness, and may explain why participants did not prefer to go on, or why no significant change in HRQOL was evident when oxygen was compared with air delivered through the same method.

Evidence for use in clinical care

Most evidence of the benefit of oxygen for breathlessness pertains to symptoms noted during standardised exercise testing in the laboratory setting. The oxygen effect during domiciliary treatment in daily life was smaller and more uncertain (SMD -0.12, 95% CI -0.39 to 0.15). More recent double-blinded randomised controlled trials (RCTs) of oxygen compared with medical air have found no statistically or clinically relevant effects of domiciliary/ambulatory oxygen on breathlessness in daily life (Abernethy 2010; Moore 2011). Less efficacy of domiciliary oxygen might reflect insufficient adherence to therapy or low physical activity due to deconditioning, or the fact that breathlessness in daily life is not assessed at a comparable time point or after a standardised workload. A

patient who benefits from oxygen (decreased breathlessness at a given workload and improved exercise capacity) might increase his/her activity up to maximal tolerable levels of breathlessness. We found that the level of breathlessness at peak exercise did not seem to be affected by oxygen. When breathlessness is recalled in daily life, reported symptom level might therefore be similar between people receiving oxygen and those given air, even if oxygen would in fact be beneficial in some patients. Whether palliative oxygen in the domiciliary setting is beneficial remains unclear. We found no evidence to show that oxygen improved HRQOL, but the data were limited.

Quality of the evidence

We rated the quality of evidence for the effect of oxygen compared with air on breathlessness as low overall upon completing a GRADE assessment (Summary of findings for the main comparison). Most evidence pertained to breathlessness measured during a standardised exercise test (moderate-quality evidence), whereas evidence was limited for breathlessness during daily life (low-quality evidence). We rated the quality of evidence showing an effect of oxygen on HRQOL as low (Summary of findings for the main comparison).

Potential biases in the review process

Limitations of this systematic review and meta-analysis mainly reflect the heterogeneity and methodological limitations of the currently available body of literature. Although we excluded studies of participants already qualifying for home oxygen therapy according to current guidelines, the review population still included a wide range of baseline oxygen saturation/partial pressure of oxygen (PaO_2). This variability could affect our results if a relationship is found between oxygen saturation and effects of oxygen on breathlessness. We addressed this issue by performing a subgroup analysis based on baseline PaO_2 ($\geq$ 9.3 kPa) and obtained consistent findings. Additionally, baseline breathlessness and physical capacity were often insufficiently reported. The review population likely included participants with varied perceptions of breathlessness and physical capacity.

We explored potential bias due to methodological limitations by excluding studies with high risk for any bias category; this yielded consistent findings. A possible limitation of this review is that many studies did not report data on participants dropping out or withdrawing from the study. Reporting of data only for participants who completed the trial might have introduced selection bias.

Palliative oxygen is prescribed most commonly for seriously ill patients nearing the end of life; however, these patients are not likely to participate in randomised trials, especially studies involving an exercise test. The applicability of review findings to all individuals with chronic obstructive pulmonary disease (COPD) who require palliative oxygen is unclear.

Effects of oxygen on breathlessness were driven in part by five outlier findings among studies with small sample sizes/low levels of precision. This asymmetry in the funnel plot might indicate the presence of publication bias. When we excluded the outliers, the oxygen effect became somewhat smaller (SMD -0.24, 95% CI -0.34 to -0.15).

Although the funnel plot indicated potential publication bias, we did not downgrade the quality of the evidence, as a sensitivity analysis excluding outlying studies yielded similar findings.

Agreements and disagreements with other studies or reviews

Compared with the 2011 version of this review (Uronis 2011; Uronis 2015), we have included an additional 14 studies (493 participants) in this update. The finding of the main analysis of breathlessness is consistent with the previous estimate but is more precise because we included more studies. Subgroup analyses by short burst and by oxygen dose were also in agreement with those of the previous review. Novel subgroup analyses in the present review show that evidence of effects of oxygen pertains mostly to breathlessness during exercise tests performed in the laboratory standardised rehabilitation training setting. Evidence is less consistent and of low quality for effects of supplemental oxygen during daily life. The novel analysis of HRQOL showed no clear effect of supplemental oxygen compared with air on quality of life.

Ameer 2014 performed a Cochrane meta-analysis (four studies; 331 participants) of the effects of ambulatory oxygen therapy given for two weeks or longer on breathlessness and HRQOL in the home setting. When compared with air or no therapy, ambulatory oxygen therapy was associated with a small reduction in breathlessness as measured on the Borg scale (mean difference 0.28, 95% CI, 0.10 to 0.45). This finding is consistent with our finding in the non-laboratory setting. The analysis of breathlessness performed by Ameer 2014 included only three studies (McDonald 1995; Eaton 2002; Nonoyama 2007), which we also included in the present review. Effects on HRQOL as noted in Ameer 2014 were inconsistent, with mean improvements in breathlessness and fatigue domains but were not related to emotional function or mastery. Small or inconsistent effects of supplemental oxygen on HRQOL and lack of clear effect on exercise capacity in Ameer 2014 support the present conclusion that the evidence base for supplemental oxygen therapy during daily life is limited.

Findings of this review are consistent with recent British Thoracic Society (BTS) guidelines stating that although ambulatory oxygen therapy should be offered to patients for use during exercise in a pulmonary rehabilitation programme, it "should not be routinely offered to patients who are not eligible for LTOT" (Hardinge 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Oxygen given continuously during exercise or activity can relieve breathlessness in patients with COPD who have no or mild hypoxaemia and would not qualify for long-term oxygen therapy. Evidence was of moderate quality for breathlessness during exercise testing in the laboratory setting and of low quality for effects on breathlessness during daily life. It is not clear whether the reduction in breathlessness shown in the laboratory setting translates into a clinically important benefit, and no evidence supports a clinically important benefit from oxygen for breathlessness in daily life. Short-burst oxygen therapy given before exercise had no effect and should not be used.

Clinical recommendations

Based on the present findings, supplemental oxygen therapy is not a first-line treatment for patients with breathlessness. Management of underlying disease(s) should be optimised. Evidence-based symptomatic treatment should include individualised rehabilitation training (McCarthy 2015), the fan and low-dose opioids (Ekstrom 2015a; Ekstrom 2015b; Hardinge 2015). In patients with intractable breathlessness despite these interventions, a trial of supplemental oxygen could be considered. Guidelines recommend that palliative oxygen should be evaluated only in patients with hypoxaemia (saturation < 92%) at rest (Hardinge 2015). We found that the oxygen effect was similar in studies with mean $PaO_2 \geq 9.3$ kPa compared with $PaO_2 < 9.3$ kPa, and that a trial of supplemental oxygen might be reasonable in patients without resting hypoxaemia, especially in the presence of hypoxaemia during limited exertion. Evaluation of the potential benefit of ambulatory oxygen should involve the patient's levels of physical capacity and activity, along with the benefits of oxygen for breathlessness and physical capacity in a standardised test such as the six-minute walking test (6MWT) when compared with air (Hardinge 2015). Patients who perceive decreased breathlessness when receiving oxygen most often experience this effect within two to three days of the start of treatment (Abernethy 2010). Therefore, palliative oxygen therapy should be evaluated after a few days and withdrawn if patients do not perceive benefit.

Patient quality of life (QOL) factors such as convenience and adverse consequences should be considered in the decision whether to prescribe oxygen as treatment for patients with breathlessness who may already be burdened by their illness and other life changes prominent in the advanced illness setting.

Finally, in considering these results, one must be sure to remember the downsides of administering oxygen. Oxygen is costly, and, with current stresses on healthcare systems in many countries, this needs to be taken into account. Evidence of the effect of supplemental oxygen on HRQOL is lacking.

In conclusion, we are moderately confident that oxygen can relieve breathlessness when given during exercise to mildly hypoxaemic and non-hypoxaemic people with COPD who would not otherwise qualify for home oxygen therapy. Most evidence pertains to acute effects during exercise testing; evidence of long-term effects of oxygen during daily life is less consistent. Findings show that oxygen did not affect HRQOL.

Implications for research

Current findings on the effect of oxygen therapy versus air have several important implications for research. First, oxygen affected breathlessness measured only at iso-time, not at peak exercise. This confirms the importance of measuring breathlessness at iso-time with comparable workloads in mechanistic studies and interventional trials.

Although this review confirms that oxygen can decrease exertional breathlessness in the laboratory setting, studies should focus on effects of domiciliary and ambulatory oxygen in clinical and daily life settings. Studies on effects of oxygen on HRQOL and on different aspects (dimensions) of breathlessness (Laviolette 2014) are needed, and investigators should identify optimal doses and routes of oxygen administration, while determining which patients are most likely to receive beneficial symptomatic effects of oxygen. Studies of symptomatic benefit should also account for changes in physical capacity and activity to explore whether oxygen given during daily living could allow increased exercise activity, although it might not affect reported breathlessness scores. Tools for measuring physical activity in COPD were recently validated (Gimeno-Santos 2015).

We found that adverse events were insufficiently assessed and/or reported. The first population-based longitudinal study of the risk of burn injury during LTOT was published only recently (Tanash 2015). Studies quantifying adverse events, patient burden and potential risks associated with supplemental oxygen therapy are needed to determine the net clinical benefit of palliative oxygen.

ACKNOWLEDGEMENTS

We would like to thank Dr Hope Uronis, Duke Medical Center, Durham, North Carolina, USA, for her work with the review published in 2011, as well as Dr Emma J Dennett and Mrs Liz Stovold, Cochrane Airways Group, for their assistance with subsequent MEDLINE/Embase/CENTRAL searches and the review process.

Professor Phillippa Poole was the Editor for this review and commented critically on the review.

The Background and Methods sections of this review are based on a standard template used by Cochrane Airways.

This project was supported by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Abernethy 2010 *{published and unpublished data}*
Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE 2nd, Marcello J, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet* 2010;**376**(9743):784–93. [4456812]

Bruni 2012a *{published data only}*
Bruni GI, Gigliotti F, Binazzi B, Romagnoli I, Duranti R, Scano G. Dyspnea, chest wall hyperinflation, and rib cage distortion in exercising patients with chronic obstructive pulmonary disease. *Medicine and Science in Sports and Exercise* 2012;**44**(6):1049–56. [4456814]

Bruni 2012b *{published data only}*
Bruni GI, Gigliotti F, Binazzi B, Romagnoli I, Duranti R, Scano G. Dyspnea, chest wall hyperinflation, and rib cage distortion in exercising patients with chronic obstructive pulmonary disease. *Medicine and Science in Sports and Exercise* 2012;**44**(6):1049–56. [4456816]

Davidson 1988 *{published data only}*
Davidson AC, Leach R, George RJD, Geddes DM. Supplemental oxygen and exercise ability in chronic obstructive pulmonary disease. *Thorax* 1988;**43**:965–71. [3216363]

Dean 1992 *{published data only}*
Dean NC, Brown JK, Himelman RB, Doherty JJ, Gold WM, Stulbarg MS. Oxygen may improve dyspnea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. *American Review of Respiratory Disease* 1992;**146**:941–5. [3216365]

Dyer 2012 *{published data only}*
Dyer F, Bott J. Ambulatory oxygen improves the effectiveness of pulmonary rehabilitation (PR) In selected patients [Abstract]. American Thoracic Society International Conference; 2010 May 14-19; New Orleans. 2010:A3763. [4456817]
* Dyer F, Callaghan J, Cheema K, Bott J. Ambulatory oxygen improves the effectiveness of pulmonary rehabilitation in selected patients with chronic obstructive pulmonary disease. *Chronic Respiratory Disease* 2012;**9**(2):83–91. [4456818]
Dyer FJ. Ambulatory oxygen improves the effectiveness of pulmonary rehabilitation (PR) in selected patients [Abstract]. *Thorax* 2010;**65**:S71. [4456819]

Eaton 2002 *{published data only}*
Eaton T, Garret JE, Young P, Fergusson W, Kolbe J, Rudkin S, et al. Ambulatory oxygen improves quality of life of COPD patients: a randomised controlled study. *European Respiratory Journal* 2002;**20**(2):306–12. [3216369]

Eaton 2006 *{published data only}*
Eaton T, Fergusson W, Kolbe J, Lewis CA, West T. Short-burst oxygen therapy for COPD patients: a 6-month randomised, controlled trial. *European Respiratory Journal* 2006;**27**(4):697–704. [3216371]

Emtner 2003a *{published data only}*
* Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in non-hypoxemic chronic obstructive pulmonary disease patients. *American Journal of Respiriatory and Critical Care Medicine* 2003;**168**(9):1034–42. [4456821]
Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Online supplement to 'Benefits of supplemental oxygen in exercise training in non-hypoxemic chronic obstructive pulmonary disease patients'. http://ajrccm.atsjournals.org/cgi/data/168/9/1034/DC1/1 (accessed 21 August 2008). [4456822]

Emtner 2003b *{published data only}*
* Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in non-hypoxemic chronic obstructive pulmonary disease patients. *American Journal of Respiratory and Critical Care Medicine* 2003;**168**(9):1034–42. [4456824]
Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Online supplement to 'Benefits of supplemental oxygen in exercise training in non-hypoxemic chronic obstructive pulmonary disease patients'. http://ajrccm.atsjournals.org/cgi/data/168/9/1034/DC1/1 (accessed 21 August 2008). [4456825]

Eves 2006 *{published data only}*
Eves ND, Petersen SR, Haykowsky MJ, Wong EY, Jones RL. Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2006;**174**(7):763–71. [3216379]

Haidl 2004 *{published data only}*
Haidl P, Clement C, Wiese C, Dellweg D, Kohler D. Long-term oxygen therapy stops the natural decline of endurance in COPD patients with reversible hypercapnia. *Respiration* 2004;**71**:342–7. [3216383]

Ishimine 1995 *{published data only}*
Ishimine A, Saito T, Nishimura S, Nakano G, Miyamoto K, Kawakami Y. The effect of oxygen supplementation during exercise in COPD patients with PaO2 over 60 Torr. *Japanese Journal of Chest Disease* 1995;**33**:510–8. [3216385]

Jolly 2001a *{published data only}*
Jolly EC, Di Boscio V, Aguirre L, Luna CM, Berensztein S, Gene RJ. Effects of supplemental oxygen during activity in patients with advanced COPD without severe resting hypoxemia. *Chest* 2001;**120**:437–43. [4456827]

Jolly 2001b *{published data only}*
Jolly EC, Di Boscio V, Aguirre L, Luna CM, Berensztein S, Gene RJ. Effects of supplemental oxygen during activity in patients with advanced COPD without severe resting hypoxemia. *Chest* 2001;**120**:437–43. [4456829]

Killen 2000 *{published data only}*
Killen JWW, Corris PA. A pragmatic assessment of the placement of oxygen when given for exercise induced dyspnea. *Thorax* 2000;**55**:544–6. [3216391]

Knebel 2000 *{published data only}*
Knebel AR, Bentz E, Barnes P. Dyspnea management in alpha-1 antitrypsin deficiency: effect of oxygen administration. *Nursing Research* 2000;**49**(6):333–8. [3216393]

Kurihara 1989 *{published data only}*
Kurihara N, Fujimoto S, Kuono M, Futoda K, Hirata K, Takeda C. Exercise induced hypoxemia and exercise tolerance in patients with COPD and the benefits of oxygen supplementation. *Japanese Journal of Chest Disease* 1989;**26**: 155–62. [4456830]

Laude 2006 *{published data only}*
Laude EA, Duffy NC, Baveystock C, Dougill B, Campbell MJ, Lawson R, et al. The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2006;**173**(8):865–70. [3216397]

Leach 1992 *{published data only}*
Leach RM, Davidson AC, Chinn S, Twort CHC, Cameron IR, Bateman NT. Portable liquid oxygen and exercise ability in severe respiratory disability. *Thorax* 1992;**47**:781–9. [3216399]

Lewis 2003 *{published data only}*
Lewis CA, Eaton TE, Young P, Kolbe J. Short-burst oxygen immediately before and after exercise is ineffective in non-hypoxic COPD patients. *European Respiratory Journal* 2003;**22**(4):584–8. [3216401]

Maltais 2001 *{published data only}*
Maltais F, Simon M, Jobin J, Desmeules M, Sullivan M, Belanger M, et al. Effects of oxygen on lower limb blood flow and O2 uptake during exercise in COPD. *Medicine and Science in Sports and Exercise* 2001;**33**(6):916–22. [3216403]

McDonald 1995 *{published data only}*
McDonald CF, Blyth DM, Lazarus MD, Marschner I, Barter CE. Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia. *American Journal of Respiratory and Critical Care Medicine* 1995;**152**:1616–9. [3216405]

McKeon 1988a *{published data only}*
McKeon JL, Murree-Allen K, Saunders NA. Effects of breathing supplemental oxygen before progressive exercise in patients with chronic obstructive lung disease. *Thorax* 1988;**43**(1):53–6. [3216407]

McKeon 1988b *{published data only}*
McKeon JL, Tomlinson JC, Tarrant EP, Mitchell CA. Portable oxygen in patients with severe chronic obstructive pulmonary disease. *Australia and New Zealand Journal of Medicine* 1988;**18**(2):125–9. [3216409]

Miki 2012 *{published data only}*
Miki K, Maekura R, Hiraga T, Kitada S, Miki M, Yoshimura K, et al. Effects of oxygen on exertional dyspnoea and exercise performance in patients with chronic obstructive pulmonary disease. *Respirology (Carlton, Vic)* 2012;**17**(1): 149–54. [3216411]

Moore 2009 *{published data only}*
Moore R, Berlowitz D, Pretto J, Brazzale D, Denehy L, Jackson B, et al. Acute effects of hyperoxia on resting pattern of ventilation and dyspnoea in COPD. *Respirology* 2009;**14**(4):545–50. [3216413]

Moore 2011 *{published data only}*
* Moore RP, Berlowitz DJ, Denehy L, Pretto JJ, Brazzale DJ, Sharpe K, et al. A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. *Thorax* 2011;**66**(1):32–7. [4456831]
Moore RP, Berlowitz R, Denehy D, Pretto L, Brazzale J, Sharpe D, et al. Domiciliary ambulatory oxygen is not beneficial in patients with COPD and mild resting hypoxaemia [Abstract]. *American Journal of Respiratory and Critical Care Medicine* 2010;**181**:[P4380]. [4456832]

Nandi 2003 *{published data only}*
* Nandi K, Smith AA, Crawford A, MacRae KD, Garrod R, Seed WA, et al. Oxygen supplementation before or after submaximal exercise in patients with chronic obstructive pulmonary disease. *Thorax* 2003;**58**:670–3. [3216417]
Smith AA, Nandi K, Crawford A, Garrod R, MacRae KD, Roberts CM, et al. Exercise intolerance, hypoxaemia and breathlessness in COPD: does pre-dosing with oxygen actually help?. *American Journal of Respiratory and Critical Care Medicine* 2001;**163**(Suppl 5):A501. [3216418]

Nonoyama 2007 *{published data only}*
Nonoyama ML. Effect of oxygen in COPD patients with transient exertional hypoxemia [Dissertation]. Dissertation Abstracts International 2010; Vol. 70, issue 10–B:6153. [4456835]
Nonoyama ML, Brooks D, Guyatt GH, Goldstein RS. Ambulatory gas usage in patients with chronic obstructive pulmonary disease and exertional hypoxemia [Abstract].

Journal of Cardiopulmonary Rehabilitation and Prevention. 2008; Vol. 28, issue 5:323–9. [4456833]
* Nonoyama ML, Brooks D, Guyatt GH, Goldstein RS. Effect of oxygen on health quality of life in patients with chronic obstructive pulmonary disease with transient exertional hypoxemia. *American Journal of Respiratory and Critical Care Medicine* 2007;**176**(4):343–9. [4456834]

O'Donnell 1997 ***{published data only}***
O'Donnell DE, Bain DJ, Webb KA. Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. *American Journal of Respiratory and Critical Care Medicine* 1997;**155**(2):530–5. [3216422]

O'Driscoll 2011 ***{published data only}***
O'Driscoll BR, Neill J, Pulakal S, Turkington PM. A crossover study of short burst oxygen therapy (SBOT) for the relief of exercise-induced breathlessness in severe COPD. *BMC Pulmonary Medicine* 2011;**11**:23. [4456836]

Oliveira 2012a ***{published and unpublished data}***
Oliveira MF, Rodrigues MK, Treptow E, Cunha TM, Ferreira EM, Neder JA. Effects of oxygen supplementation on cerebral oxygenation during exercise in chronic obstructive pulmonary disease patients not entitled to long-term oxygen therapy. *Clinical Physiology and Functional Imaging* 2012;**32**(1):52–8. [4456838]

Oliveira 2012b ***{published and unpublished data}***
Oliveira MF, Rodrigues MK, Treptow E, Cunha TM, Ferreira EM, Neder JA. Effects of oxygen supplementation on cerebral oxygenation during exercise in chronic obstructive pulmonary disease patients not entitled to long-term oxygen therapy. *Clinical Physiology and Functional Imaging* 2012;**32**(1):52–8. [4456840]

Ringbaek 2013 ***{published and unpublished data}***
Ringbaek T, Martinez G, Lange P. The long-term effect of ambulatory oxygen in normoxaemic COPD patients: a randomised study. *Chronic Respiratory Disease* 2013;**10**(2): 77–84. [4456841]

Rooyackers 1997 ***{published data only}***
Rooyackers JM, Dekhuijzen PNR, Van Herwaarden CLA, Folgering HTM. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *European Respiratory Journal* 1997;**10**:1278–84. [4456843]

Rooyackers 1997a ***{published data only}***
Rooyackers JM, Dekhuijzen PNR, Van Herwaarden CLA, Folgering HTM. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *European Respiratory Journal* 1997;**10**(6):1278–84. [4456845]

Rooyackers 1997b ***{published data only}***
Rooyackers JM, Dekhuijzen PNR, Van Herwaarden CLA, Folgering HTM. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *European Respiratory Journal* 1997;**10**:1278–84. [4456847]

Scorsone 2010 ***{published data only}***
Scorsone D, Bartolini S, Saporiti R, Braido F, Baroffio M, Pellegrino R, et al. Does a low-density gas mixture or oxygen supplementation improve exercise training in COPD?. *Chest* 2010;**138**(5):1133–9. [3216436]

Somfay 2001 ***{published data only}***
Somfay A, Porszasz J, Lee SM, Casaburi R. Dose-response effect of oxygen on hyperinflation and exercise endurance in non-hypoxemic COPD patients. *European Respiratory Journal* 2001;**18**(1):77–84. [3216438]

Spielmanns 2014 ***{published and unpublished data}***
Spielmanns M, Fuchs-Bergsma C, Winkler A, Fox G, Krüger S, Baum K. Effects of oxygen supply during training on subjects with COPD who are normoxemic at rest and during exercise: a blinded randomized controlled trial. *Respiratory Care* 2015;**60**:540–8. [4456848]

Swinburn 1984 ***{published data only}***
Swinburn CR, Wakefield JM, Jones PW. Relationship between ventilation and breathlessness during exercise in chronic obstructive airways disease is not altered by prevention of hypoxaemia. *Clinical Sciences* 1984;**67**: 515–9. [3216442]

Voduc 2010 ***{published data only}***
Voduc N, Tessier C, Sabri E, Fergusson D, Lavallee L, Aaron SD. Effects of oxygen on exercise duration in chronic obstructive pulmonary disease patients before and after pulmonary rehabilitation. *Canadian Respiratory Journal [Revue canadienne de pneumologie]* 2010;**17**(1):e14–e9. [4456849]

Wadell 2001 ***{published data only}***
Janaudis-Ferreira T, Henriksson-Larsen K, Lundgren R, Wadell K. Differences in training effects following training with and without supplemental oxygen in patients with COPD. *Advances in Physiotherapy* 2009;**11**(4):186–92. [4456850]
* Wadell K, Henriksson-Larsen K, Lundgren R. Physical training with and without oxygen in patients with chronic obstructive pulmonary disease and exercise-induced hypoxemia. *Journal of Rehabilitation Medicine* 2001;**33**(5): 200–5. [4456851]

Woodcock 1981 ***{published data only}***
Woodcock AA, Gross ER, Geddes DM. Oxygen relieves breathlessness in "pink puffers". *Lancet* 1981;**1**(8226): 907–9. [3216448]

References to studies excluded from this review

Alexandre 2010 ***{published data only}***
Alexandre P, Jaume S, Angel R, Aina N, Amanda, I, Alvar A. Oxygen therapy decreases systemic inflammation in patients with chronic obstructive pulmonary disease and hypoxemia [Abstract]. European Respiratory Journal. 2010:[376]. [4456852]

Arnold 2008 ***{published data only}***
Arnold B. Oxygen for COPD patients [Abstract]. Journal of Pain & Palliative Care Pharmacotherapy. 2008; Vol. 22, issue 3:228–9. [4456853]

Balkissoon 2006 ***{published data only}***
Balkissoon R. The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease:

a randomized crossover trial. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2006;**3**:173–4. [3216454]

Bjørgen 2009 ***{published data only}***
Bjørgen S, Helgerud J, Husby V, Steinshamn S, Richadson RR, Hoff J. Aerobic high intensity one-legged interval cycling improves peak oxygen uptake in chronic obstructive pulmonary disease patients; no additional effect from hyperoxia. *International Journal of Sports Medicine* 2009;**30** (12):872–8. [4456854]

Bradley 1978 ***{published data only}***
Bradley BL, Garner AE, Billiu D, Mestas JM, Forman J. Oxygen-assisted exercise in chronic obstructive lung disease. *American Review of Respiratory Disease* 1978;**118**:239–43. [3216458]

Bye 1985 ***{published data only}***
Bye PTP, Esau SA, Levy RD, Shiner RJ, Macklem PT, Martin JG, et al. Ventilatory muscle function during exercise in air and oxygen in patients with chronic air-flow limitation. *American Review of Respiratory Disease* 1985; **132**:236–40. [3216460]

Campbell 2013 ***{published data only}***
Campbell M, Yarandi H. The benefit of routine oxygen administration for terminally ill patients who are near death [Abstract]. Journal of Pain and Symptom Management. Conference: Annual Assembly of the American Academy of Hospice and Palliative Medicine and the Hospice and Palliative Nurses Association, 2012, Denver, CO, United States. 2012; Vol. 43, issue 2:336–7. [4456855]
* Campbell ML, Yarandi H, Dove-Medows E. Oxygen is nonbeneficial for most patients who are near death. *Journal of Pain and Symptom Management* 2013;**45**(3):517–23. [4456856]

Caspersen 2012 ***{published data only}***
Caspersen NF, Karlsen CG, Edvardsen A, Skumlien S. Reduced exertional dyspnea with supplemental oxygen in patients with COPD - Characteristics of responders and non-responders [Abstract]. *European Respiratory Journal* 2012;**40**(Suppl 56):548s [3094]. [4456857]

Criner 1987 ***{published data only}***
Criner GJ, Celli BR. Ventilatory muscle recruitment in exercise with O2 in obstructed patients with mild hypoxemia. *Journal of Applied Physiology* 1987;**63**:195–200. [3216468]

Cuvelier 2002 ***{published data only}***
Cuvelier A, Nuir J-F, Chakroun N. Refillable oxygen cylinders may be an alternative for ambulatory oxygen therapy in COPD. *Chest* 2002;**122**:451–6. [3216470]

Edvardsen 2007 ***{published data only}***
Edvardsen A, Christensen CC, Skjonsberg OH, Ryg M. Effect of high dose oxygen on dyspnea and exercise tolerance in patients with COPD given LTOT. *European Respiratory Journal* 2007;**30**(51):513s [E3078]. [3216474]

Evans 1986 ***{published data only}***
Evans TW, Waterhouse JC, Carter A, Nicholl JF, Howard P. Short burst oxygen treatment for breathlessness in chronic obstructive airways disease. *Thorax* 1986;**41**:611–5. [3216476]

Fraser 2013 ***{published data only}***
Fraser JF, Corley A, Spooner A, Dunster KR. Nasal high flow with supplemental oxygen modifies ventilation and reduces tissue CO2 In COPD patients. *American Journal of Respiratory and Critical Care Medicine* 2013;**187**:A4381. [4456858]

Fujimoto 2002 ***{published data only}***
Fujimoto K, Matsuzawa Y, Yamaguchi S, Koizumi T, Kubo K. Benefits of oxygen on exercise performance and pulmonary hemodynamics in patients with COPD with mild hypoxemia. *Chest* 2002;**122**:457–63. [3216480]

Garrod 2000 ***{published data only}***
Garrod R, Paul EA, Wedzicha JA. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. *Thorax* 2000;**55**:539–43. [3216482]

Gosselin 2004 ***{published data only}***
Gosselin N, Durand F, Poulain M, Lambert K, Ceugniet F, Prefaut C, et al. Effect of acute hyperoxia during exercise on quadriceps electrical activity in active COPD patients. *Acta Physiologica Scandinavica* 2004;**181**:333–43. [3216484]

Heinzelmann 2011 ***{published data only}***
Heinzelmann I, Kenn K. Characteristics of 'oxygen responder' before and after rehabilitation [Abstract]. *American Journal of Respiratory and Critical Care Medicine* 2010;**181**:A3580. [4456859]
* Heinzelmann I, Kenn K. The influence of O2 on exercise capacity (6-minute-walking-distance, 6MWD) in COPD [Abstract]. *European Respiratory Journal* 2011;**38(Suppl 55)**. [4456860]

Helgerud 2010 ***{published data only}***
Helgerud J, Bjorgen S, Karlsen T, Husby VS, Steinshamn S, Richardson RS, et al. Hyperoxic interval training in chronic obstructive pulmonary disease patients with oxygen desaturation at peak exercise. *Scandinavian Journal of Medicine & Science in Sports* 2010;**20**(1):e170–6. [4456861]

King 1973 ***{published data only}***
King AJ, Cooke NJ, Leitch AG, Flenley DC. The effects of 30% oxygen on the respiratory response to treadmill exercise in chronic respiratory failure. *Clinical Science* 1973; **44**:151–62. [3216494]

King 2012 ***{published data only}***
King C, Young P, Fergusson W, Eaton T, Kolbe J. No benefit from short-burst oxygen therapy for dyspnoeic COPD patients after activities of daily living [Abstract]. 2012 Annual Scientific Meetings of the Thoracic Society of Australia and New Zealand and the Australian and New Zealand Society of Respiratory Science; 2012 Mar 30-Apr 4; Canberra. 2012, issue Suppl 1:59. [4456862]

Lane 1987 ***{published data only}***
Lane R, Cockcroft A, Adams L, Guz A. Arterial oxygen saturation and breathlessness in patients with chronic obstructive airways disease. *Clinical Science* 1987;**72**:693–8. [3216498]

Leggett 1977 *{published data only}*
Leggett RJE, Flenley DC. Portable oxygen and exercise tolerance in patients with chronic hypoxic cor pulmonale. *British Medical Journal* 1977;**2**(6079):84–6. [3216500]

Lellouche 2011 *{published data only}*
Lellouche F, Maltais F, Bouchard PA, Brouillard C, L'Her E. Free O2: closed-loop automatic titration of oxygen flow based on SpO2 evaluation in COPD patients during endurance shuttle walking [Abstract]. Canadian Respiratory Journal [Revue canadienne de pneumologie]. 2011; Vol. 18:22A. [4456863]

Light 1989 *{published data only}*
Light RW, Mahutte CK, Stansbury DW, Fischer CE, Brown SE. Relationship between improvement in exercise performance with supplemental oxygen and hypoxic ventilatory drive in patients with chronic airflow obstruction. *Chest* 1989;**95**:751–6. [3216504]

Liss 1988 *{published data only}*
Liss HP, Grant BJB. The effect of nasal flow on breathlessness in patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 1988;**137**:1285–8. [3216506]

Lock 1992 *{published data only}*
Lock SH, Blower G, Prynne M, Wedzicha JA. Comparison of liquid and gaseous oxygen for domiciliary portable use. *Thorax* 1992;**47**:98–100. [3216508]

Maldonado 2014 *{published data only}*
Maldonado D, Gonzalez-Garcia M, Barrero M, Jaramillo C, Casas A. Exercise endurance in chronic obstructive pulmonary disease patients at an altitude of 2640 meters breathing air and oxygen (FIO2 28% and 35%): a randomized crossover trial. *COPD* 2014;**11**(4):401–6. [4456864]

Mannix 1992 *{published data only}*
Mannix ET, Manfredi F, Palange P, Dowdeswell IR, Farber M. Oxygen may lower the O2 cost of ventilation in chronic obstructive lung disease. *Chest* 1992;**101**:910–5. [3216512]

Marques-Magallanes 1998 *{published data only}*
Marques-Magallanes JA, Storer TW, Cooper CB. Treadmill exercise duration and dyspnea recovery time in chronic obstructive pulmonary disease: effects of oxygen breathing and repeated testing. *Respiratory Medicine* 1998;**92**:735–8. [3216514]

Matsuzawa *{published data only}*
Matsuzawa Y, Kubo K, Fujimoto K, Eda S, Yamaguchi S, Koizumi T, et al. Acute effects of oxygen on dyspnea and exercise tolerance in patients with pulmonary emphysema with only mild exercise-induced oxyhemoglobin desaturation [Japanese]. *Nihon Kokyuki Gakkai Zasshi* 2000;**38**(11):831–5. [4456865]

Nasilowski 2008 *{published data only}*
Nasilowski J, Przybylowski T, Zielinski J, Chazan R. Comparing supplementary oxygen benefits from a portable oxygen concentrator and a liquid oxygen portable device during a walk test in COPD patients on long-term oxygen therapy. *Respiratory Medicine* 2008;**102**(7):1021–5. [3216520]

Nguyen 2008 *{published data only}*
Nguyen HQ, Donesky-Cuenco D, Wolpin S, Reinke LF, Benditt JO, Paul SM, et al. Randomized controlled trial of an internet-based versus face-to-face dyspnea self-management program for patients with chronic obstructive pulmonary disease: pilot study. *Journal of Medical Internet Research* 2008;**10**(2):e9. [3216522]

Noseda 1997 *{published data only}*
Noseda A, Carpiaux JP, Markstein C, Meyvaert A, de Maertelaer V. Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. *European Respiratory Journal* 1997;**10**:1079–83. [3216528]

O'Donnell 2001 *{published data only}*
O'Donnell DE, D'Arsigny C, Webb KA. Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2001;**163**: 892–8. [3216530]

O'Driscoll 2003 *{published data only}*
O'Driscoll R, Wolstenholme RJ, Pilling A, Bassett C, Singer M, Bellingan G, et al. The use of oxygen in acute exacerbations of chronic obstructive pulmonary disease: a prospective audit of pre-hospital and hospital emergency management. *Clinical Medicine* 2003;**3**:183–6. [3216532]

O'Driscoll 2007 *{published data only}*
O'Driscoll BR, Siddiq Pulakal A, Neill J, Turkington P. Does short burst oxygen therapy (SBOT) relieve breathlessness after exercise in patients with severe COPD who are not hypoxemic at rest. *European Respiratory Journal* 2007;**30**(5): 72s [P579]. [3216534]

O'Neill 2006 *{published data only}*
O'Neill B, Bradley JM, Mckevitt AM, Bradbury I, Riley M, MacMahon J. Do patients prescribed short-burst oxygen therapy meet criteria for ambulatory oxygen?. *International Journal of Clinical Practice* 2006;**60**:146–9. [3216536]

Ouyang 2006 *{published data only}*
Ouyang XH, Yin R, Zhang Y. Effects of shenmai injection on the clinical efficacy of noninvasive ventilation in patients with severe respiratory failure caused by chronic obstructive pulmonary disease. *Chinese Journal of Integrated Traditional and Western Medicine* 2006;**26**(7):608–11. [3216538]

Palwai 2010 *{published data only}*
Palwai A, Skowronski M, Coreno A, Drummond C, McFadden ER Jr. Critical comparisons of the clinical performance of oxygen-conserving devices. *American Journal of Respiratory and Critical Care Medicine* 2010;**181** (10):1061–71. [4456866]

Peters 2006 *{published data only}*
* Peters MM, Webb KA, O'Donnell DE. Combined physiological effects of bronchodilators and hyperoxia on exertional dyspnoea in normoxic COPD. *Thorax* 2006;**61**: 559–67. [4456867]
Peters MM, Webb KA, O'Donnell DE. The effects of supplemental oxygen and bronchodilators on exertional

dyspnea and exercise performance in COPD. American Thoracic Society International Conference; 2005 May 20-25; San Diego. 2005:Poster A58. [4456868]

Raimondi 1970 *{published data only}*
Raimondi AC, Edwards RHT, Denison DM, Leaver DG, Spencer RG, Siddorn JA. Exercise tolerance breathing a low density gas mixture, 35% oxygen and air in patients with chronic obstructive bronchitis. *Clinical Science* 1970;**39**: 675–85. [3216545]

Roberts 1996 *{published data only}*
Roberts CM, Bell J, Wedzicha JA. Comparison of the efficacy of a demand oxygen delivery system with continuous low flow oxygen in subjects with stable COPD and severe oxygen desaturation on walking. *Thorax* 1996;**51**:831–4. [3216547]

Sandland 2008a *{published data only}*
Sandland CJ, Morgan MD, Singh SJ. Patterns of domestic activity and ambulatory oxygen usage in COPD. *Chest* 2008;**134**(4):753–60. [3216551]

Sandland 2008b *{published data only}*
Sandland CJ, Morgan MDL, Singh SJ. Detecting oxygen desaturation in patients with COPD: incremental versus endurance shuttle walking. *Respiratory Medicine* 2008;**102** (8):1148–52. [3216553]

Sforza 2010 *{published data only}*
Riario Sforza GG, Incorvaia C, Carminati A, Paterniti F, Pessina L, Caligiuri R, et al. Effects of oxygen supplementation during pulmonary rehabilitation in COPD normoxemic patients [Abstract]. European Respiratory Journal. 2010:[P626]. [4456869]

Stein 1982 *{published data only}*
Stein DA, Bradley BL, Miller WC. Mechanisms of oxygen effects on exercise in patients with chronic obstructive pulmonary disease. *Chest* 1982;**81**:6–10. [3216559]

Stevenson 2004 *{published data only}*
Stevenson NJ, Calverley PM. Effect of oxygen on recovery from maximal exercise in patients with chronic obstructive pulmonary disease. *Thorax* 2004;**59**:668–72. [3216561]

Swinburn 1991 *{published data only}*
Swinburn CR, Mould H, Stone TN, Corris PA, Gibson GJ. Symptomatic benefit of supplemental oxygen in hypoxemic patients with chronic lung disease. *American Review of Respiratory Disease* 1991;**143**:913–5. [3216563]

Vyas 1971 *{published data only}*
Vyas MN, Banister EW, Morton JW, Grzybowski S. Response to exercise in patients with chronic airway obstruction. *American Review of Respiratory Disease* 1971; **103**:401–12. [3216565]

Waterhouse 1983 *{published data only}*
Waterhouse JC, Howard P. Breathlessness and portable oxygen in chronic obstructive airways disease. *Thorax* 1983; **38**:302–6. [3216567]

Wedzicha 2006 *{published data only}*
Wedzicha JA. Heliox in chronic obstructive pulmonary disease: lightening the airflow. *American Journal of Respiratory and Critical Care Medicine* 2006;**173**:825–6. [3216569]

Womble 2010 *{published data only}*
Womble HM, Johnston RP, Schwartzstein RM, Roberts DH. The effect of supplemental oxygen on maximal consumption of oxygen and ventilatory parameters In chronic obstructive pulmonary disease [Abstract]. *American Journal of Respiratory and Critical Care Medicine* 2010;**181**: A3572. [4456870]

Womble 2012 *{published data only}*
Womble HM, Schwartzstein RM, Johnston RP, Roberts DH. Effect of therapeutic hyperoxia on maximal oxygen consumption and perioperative risk stratification in chronic obstructive pulmonary disease. *Lung* 2012;**190**:263–9. [4456871]

Additional references

Abernethy 2005
Abernethy AP, Currow DC, Frith P, Fazekas B. Prescribing palliative oxygen: a clinician survey of expected benefit and patterns of use. *Palliative Medicine* 2005;**19**(2):168–70.

Ameer 2014
Ameer F, Carson KV, Usmani ZA, Smith BJ. Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: 10.1002/14651858.CD000238.pub2]

Cranston 2005
Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD001744.pub2]

Cranston 2008
Cranston JM, Crockett A, Currow D. Oxygen therapy for dyspnoea in adults. *Cochrane Database of Systematic Reviews* 2008;**3**:CD004769.

Ekstrom 2015a
Ekstrom M, Nilsson F, Abernethy AA, Currow DC. Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease: a systematic review. *Annals of the American Thoracic Society* 2015;**12(7)**:1079–92.

Ekstrom 2015b
Ekstrom MP, Abernethy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. *BMJ* 2015;**349**:g7617.

Follmann 1992
Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology* 1992;**45**(7):769–73.

Gimeno-Santos 2015
Gimeno-Santos E, Raste Y, Demeyer H, Louvaris Z, de Jong C, Rabinovich RA, et al. The PROactive instruments to measure physical activity in patients with chronic obstructive pulmonary disease. *The European Respiratory Journal* 2015;**46**(4):988–1000.

Guyatt 2000
Guyatt GH, McKim DA, Austin P, Bryan R, Norgren J, Weaver B, et al. Appropriateness of domiciliary oxygen delivery. *Chest* 2000;**118**(5):1303–8.

Hardinge 2015
Hardinge M, Annandale J, Bourne S, Cooper B, Evans A, Freeman D, et al. British Thoracic Society guidelines for home oxygen use in adults. *Thorax* 2015;**70 Suppl 1**:i1–43.

Higgins 2011
Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**: d5928.

Johnson 2013
Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Clinically important differences in the intensity of chronic refractory breathlessness. *Journal of Pain and Symptom Management* 2013;**46**(6):957–63.

Johnson 2016
Johnson MJ, Booth S, Currow DC, Lam LT, Phillips JL. A mixed-methods, randomized, controlled feasibility trial to inform the design of a phase III trial to test the effect of the handheld fan on physical activity and carer anxiety in patients with refractory breathlessness. *Journal of Pain and Symptom Management* 2016;**51**(5):807–15.

Laviolette 2014
Laviolette L, Laveneziana P, Faculty ERSRS. Dyspnoea: a multidimensional and multidisciplinary approach. *The European Respiratory Journal* 2014;**43**(6):1750–62.

McCarthy 2015
McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD003793.pub3]

MRCWP 1981
Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981;**1**(8222):681–6.

NOTTG 1980
Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Annals of Internal Medicine* 1980;**93**(3):391–8.

Parshall 2012
Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *American Journal of Respiratory and Critical Care Medicine* 2012;**185**(4): 435–52.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Robb 2003
Robb BW, Hungness ES, Hershko DD, Warden GD, Kagan RJ. Home oxygen therapy: adjunct or risk factor?. *Journal of Burn Care and Rehabilitation* 2003;**24**:403–6.

Schwartzstein 1987
Schwartzstein RM, Lahive K, Pope A, Weinberger SE, Weiss JW. Cold facial stimulation reduces breathlessness induced in normal subjects. *American Review of Respiratory Disease* 1987;**136**(1):58–61.

Stringer 2004
Stringer E, McParland C, Hernandez P. Physician practices for prescribing supplemental oxygen in the palliative care setting. *Journal of Palliative Care* 2004;**20**(4):303–7.

Tanash 2015
Tanash HA, Huss F, Ekstrom M. The risk of burn injury during long-term oxygen therapy: a 17-year longitudinal national study in Sweden. *International Journal of Chronic Obstructive Pulmonary Disease* 2015;**10**:2479–84.

Uronis 2015
Uronis HE, Ekstrom MP, Currow DC, McCrory DC, Samsa GP, Abernethy AP. Oxygen for relief of dyspnoea in people with chronic obstructive pulmonary disease who would not qualify for home oxygen: a systematic review and meta-analysis. *Thorax* 2015;**70**(5):492–4.

Vesteng 2015
Vesteng LK, Skjørten I, Melsom M, Edvardsen A. COPD and oxygen supplementation: improvement in inspiratory capacity and dyspnea during exercise. *European Respiratory Journal* 2015;**46**:PA4603.

References to other published versions of this review

Uronis 2011
Uronis H, McCrory DC, Samsa G, Currow D, Abernethy A. Symptomatic oxygen for non-hypoxaemic chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: 10.1002/14651858.CD006429.pub2]

* *Indicates the major publication for the study*

Paper IV

Is chronic breathlessness less recognised and treated compared with chronic pain? A case-based randomised controlled trial

To the Editor:

Chronic breathlessness is a major cause of suffering in chronic obstructive pulmonary disease (COPD) [1]. Despite the impact on patients' daily lives, chronic breathlessness might be under-recognised and under-treated. No previous study has explored physicians' ability to identify chronic breathlessness in relation to other chronic symptoms.

Chronic pain, in contrast to chronic breathlessness [2], is a well-recognised clinical syndrome [3]. Measurement and treatment of pain is standard of care in many settings and is considered a basic human right [3]. It has been suggested that identification and optimal treatment of chronic breathlessness should also be recognised as a basic right [4, 5].

Evidence-based symptomatic treatment for chronic breathlessness is available, including both non-pharmacological and pharmacological interventions. The pharmacological treatment with the strongest evidence is low-dose, oral extended-release morphine [6, 7]. Observational studies report that physicians remain reluctant to prescribe opioids for relief of breathlessness in COPD patients [8–11]. A recent meta-analysis reported no evidence of clinically relevant respiratory adverse effects of low-dose opioids for chronic breathlessness [12].

We aimed to test the hypotheses that compared with chronic pain, chronic breathlessness is less likely to be recognised by physicians as needing symptomatic treatment and to receive treatment with opioids in severe COPD. The secondary aim was to compare reasons for not treating patients with opioids between chronic breathlessness and pain.

This was a double-blind, randomised (1:1), controlled, parallel-group, web-based trial using hypothetical case scenarios. The study was approved by Lund University Research Ethics Committee (Dnr: 2015/596) and prospectively registered with ClinicalTrials.gov (NCT02728674). All participants gave their informed consent. Inclusion criteria were: licensed physician; treating patients with respiratory problems in clinical practice; able to understand a case description in Swedish; not on the research team and not aware of the study's design or content; and no previous participation.

The case scenario related to a patient (59 years old, former smoker, optimally treated hypertension, medication with paracetamol and nonsteroidal anti-inflammatory drug allergy) who was diagnosed with severe COPD. The patient was optimally treated with triple inhalation therapy, vaccination against *Influenza* and *Pneumococcus* spp. and individualised pulmonary rehabilitation according to current guidelines [13]. At follow-up, the patient was said to be troubled by severe ["breathlessness" or "pain"] that markedly restricted daily activities and that had remained unchanged for at least three months. The case progressively revealed more information and questions on how the physician would manage the patient. The participant had to answer each question in order to advance to the next page and would not return to or change earlier responses.

The study endpoints were assessed in four stages.

@ERSpublications
This study highlights the need for improved assessment and management of chronic breathlessness in clinical practice http://ow.ly/S7Ua30kPmjW

Cite this article as: Ahmadi Z, Sandberg J, Shannon-Honson A, *et al*. Is chronic breathlessness less recognised and treated compared with chronic pain? A case-based randomised controlled trial. *Eur Respir J* 2018; 52: 1800887 [https://doi.org/10.1183/13993003.00887-2018].

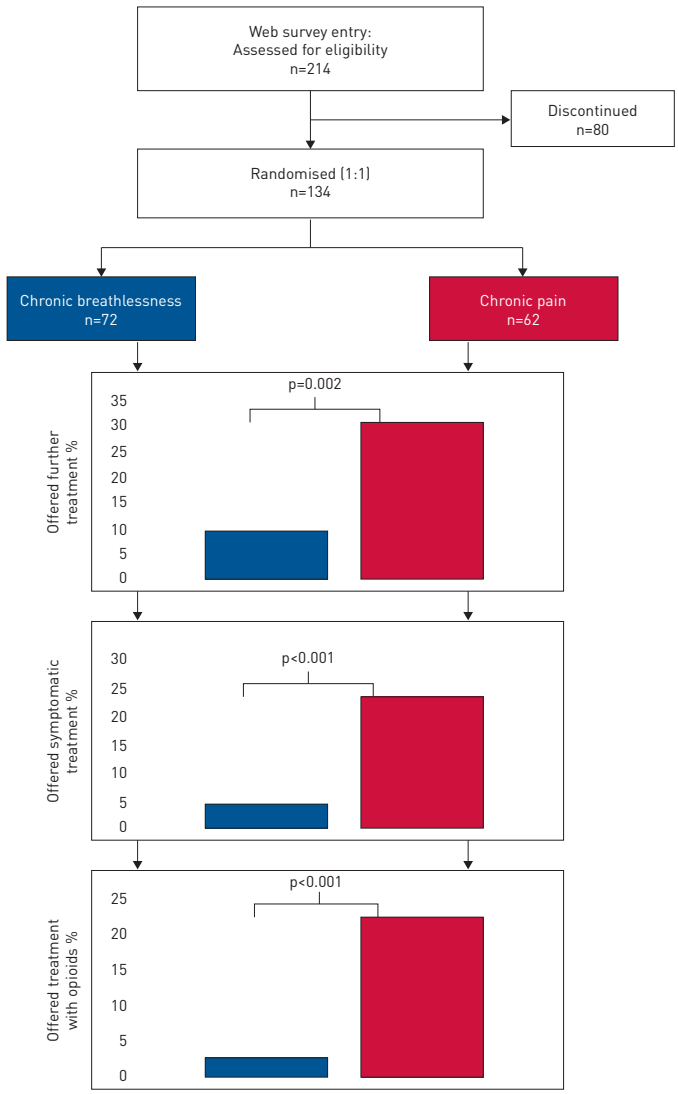


FIGURE 1 Study design and main findings.

1) Need of further treatment ("How do you manage the patient now?": "Additional diagnostic measures"; "Additional treatment"; "Active watchful waiting with follow-up visit"; or "Has optimal treatment at present, new contact if necessary".)

2) If additional treatment, type of additional treatment ("What do you want to treat additionally in the first place?": "The COPD"; "Symptoms"; or "Other".)

3) If symptoms, which symptomatic treatment ("Which treatments would you offer?": "Changed inhalation therapy"; "Intensified rehabilitation training"; "Benzodiazepines"; "Opioid, *e.g.* morphine"; "Oral steroid, *e.g.* prednisolone"; "Roflumilast (daxas)"; "Oxygen therapy"; "Theophylline"; or "Other".)

4) If not opioids, reasons for not treating with opioids.

At the end of the survey, all participants were informed that the patient had breathlessness with an intensity of 7 out of 10 and answered whether the described patient suffered from chronic breathlessness, and on how often they prescribed opioids in their clinical practice for breathlessness and pain, respectively.

The endpoints were compared between groups using chi-squared tests and multivariable logistic regression adjusted for physician seniority (resident or consultant) and present working specialty (internal medicine, primary care, pulmonary medicine or other). Statistical significance was defined as a two-tailed $p<0.025$ due to two co-primary endpoints. Analyses were performed using Stata version 14.2 (StataCorp LP; College Station, TX, USA). Given the observed proportions of 10% *versus* 30% for identifying the need for further symptomatic treatment, a sample size of 114 participants (57 per group) was required to obtain at least 80% power for the primary analysis.

From September 2016 to May 2017, a total of 134 physicians were randomised to a case with chronic breathlessness (n=72) or chronic pain (n=62; figure 1). Characteristics of the groups were well balanced; median age 42 years; 53% males; 52% worked in hospital and 46% in primary care; and the mean work experience as a physician was 11 years. For chronic breathlessness, compared with chronic pain of similar severity, significantly fewer physicians recognised the need for further treatment (10% *versus* 31%; p=0.002), fewer offered symptomatic treatment (4% *versus* 24%; p <0.001); and markedly fewer offered treatment with opioids (3% *versus* 23%; p<0.001); (figure 1).

Findings were similar in adjusted analyses; physicians were less likely to recognise the need for further treatment (OR 0.23; 95% CI 0.08–0.64), offer symptomatic treatment (OR 0.11; 95% CI 0.03–0.43) and treat with opioids (OR 0.11; 95% CI 0.02–0.51). Reasons for not treating with opioids differed markedly for breathlessness compared with pain: insufficient knowledge on usage and dosage of opioids (51% *versus* 4%; p<0.001); lack of optimal treatment guidelines (36% *versus* 17%; p=0.024); opioids considered relevant by physicians only in an end-of-life setting (31% *versus* 4%; p<0.001). However, the risk of serious adverse events was perceived as similar between the symptoms. Almost all (n=129; 96%) physicians considered that the patient suffered from chronic breathlessness. Fewer physicians prescribed opioids in their clinical practice for chronic breathlessness than for chronic pain (18% *versus* 31%; p<0.001) and markedly more physicians never prescribed opioids for breathlessness than pain (47% *versus* 17%; p<0.001).

This is the first randomised trial to evaluate potential under-recognition and under-treatment of chronic breathlessness in COPD. We found that compared with chronic pain, chronic breathlessness was markedly less likely to be recognised as needing symptomatic treatment and to receive treatment with opioids. The present findings extend previous small qualitative [9, 10] and observational data [11].

Despite that the patient was "Limited by severe ["breathlessness" or "pain"] that markedly restricted daily activities", chronic breathlessness was less likely to be identified as requiring additional treatment. There are several potential reasons for this finding. Chronic breathlessness is so common in severe respiratory disease that it might simply be considered by physicians, patients and caregivers as inevitable and part of the patient's normal life. Another potential reason is that breathlessness, despite recommendations, is rarely systematically assessed or followed-up in clinical practice [14]. The finding might also, at least partly, reflect skepticism among physicians of the availability of effective treatment for chronic breathlessness whereas pain might be considered more amenable to treatment. Main reasons for not treating with opioids were insufficient knowledge on usage and dosage of opioids and lack of optimal treatment guidelines. However, the risk of serious adverse events was perceived as similar between the symptoms.

A limitation of the study is that management decisions in clinical practice may differ from responses to a theoretical hypothetical case scenario. However, the case scenario represented a patient category and situation that is frequently encountered in the clinicians' practice, and participants were carefully instructed to answer in accordance with their usual management. The differences in symptom recognition and management in this trial were independent of the physician's working specialty and level of seniority.

For clinicians, this study highlights the need to identify symptoms and their impact more actively, and especially for chronic breathlessness; to systematically measure symptoms in daily practice and to actively consider evidence-based symptomatic treatment.

Zainab Ahmadi[1], Jacob Sandberg[2], Aaron Shannon-Honson[3], Zac Vandersman[3], David C. Currow[3] and Magnus Ekström[1,3]

[1]Dept of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University, Lund, Sweden. [2]Center for Primary Health Care Research, Dept of Clinical Sciences in Malmö, Lund University, Lund, Sweden. [3]IMPACCT, Faculty of Health, University of Technology Sydney, Ultimo, Australia.

Correspondence: Zainab Ahmadi, Dept of Clinical Sciences, Division of Respiratory Medicine and Allergology, Lund University, SE-221 00 Lund, Sweden. E-mail: zai.ahmd@gmail.com

This study is registered at ClinicalTrials.gov with identifier number NCT02728674. Additional unpublished data can be assessed by sending an e-mail to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

Received: Jan 06 2018 | Accepted after revision: June 30 2018

Acknowledgements: The authors thank the Swedish Respiratory Society, the Swedish Society of Internal Medicine, and the Swedish Society of Primary Care for help with standardising recruitment, and all physicians who participated and made this trial possible.

Author contributions: Z. Ahmadi had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Conception: M. Ekström, Z. Ahmadi; design: A. Shannon-Honson, M. Ekström, Z. Ahmadi, Z. Vandersman; acquisition of data: J. Sandberg, M. Ekström, Z. Ahmadi; analysis of data: M. Ekström, Z. Ahmadi; interpretation of data: D.C. Currow, J. Sandberg, M. Ekström, Z. Ahmadi; drafting the article: D.C. Currow, J. Sandberg, M. Ekström, Z. Ahmadi; revision for important intellectual content and approval of the version to be published: all authors. The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Support statement: Z. Ahmadi had full access to all the data in the study and had final responsibility for the decision to submit for publication. M. Ekström was supported by unrestricted grants from The Swedish Society of Medicine, the Swedish Respiratory Society, the Swedish Heart-Lung Foundation, the Scientific Committee of Blekinge County Council, and the Swedish Society for Medical Research. The funders had no influence on the design, conduct, analysis or reporting of the study. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: None declared.

References

1 Sundh J, Ekstrom M. Persistent disabling breathlessness in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2805–2812.
2 Johnson MJ, Yorke J, Hansen-Flaschen J, *et al.* Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *Eur Respir J* 2017; 49: 1602277.
3 Lohman D, Schleifer R, Amon JJ. Access to pain treatment as a human right. *BMC Med* 2010; 8: 8.
4 Currow DC, Abernethy AP, Ko DN. The active identification and management of chronic refractory breathlessness is a human right. *Thorax* 2014; 69: 393–394.
5 Basoglu M. Effective management of breathlessness: a review of potential human rights issues. *Eur Respir J* 2017; 49: 1602099.
6 Ekstrom MP, Abernethy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. *BMJ* 2015; 349: g7617.
7 Ekstrom M, Nilsson F, Abernethy AA, *et al.* Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thorac Soc* 2015; 12: 1079–1092.
8 Ahmadi Z, Bernelid E, Currow DC, *et al.* Prescription of opioids for breathlessness in end-stage COPD: a national population-based study. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2651–2657.
9 Young J, Donahue M, Farquhar M, *et al.* Using opioids to treat dyspnea in advanced COPD: attitudes and experiences of family physicians and respiratory therapists. *Can Fam Physician* 2012; 58: E401–E407.
10 Rocker G, Young J, Donahue M, *et al.* Perspectives of patients, family caregivers and physicians about the use of opioids for refractory dyspnea in advanced chronic obstructive pulmonary disease. *CMAJ* 2012; 184: E497–E504.
11 Janssen DJA, de Hosson SM, bij de Vaate E, *et al.* Attitudes toward opioids for refractory dyspnea in COPD among Dutch chest physicians. *Chron Respir Dis* 2015; 12: 85–92.
12 Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, *et al.* Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. *Eur Respir J* 2017; 50: 1701153.
13 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and Prevention of COPD 2017. Available from http://goldcopd.org Date last accessed: December 2, 2017.
14 Mularski RA, Campbell ML, Asch SM, *et al.* A review of quality of care evaluation for the palliation of dyspnea. *Am J Respir Crit Care Med* 2010; 181: 534–538.

APPENDIX 1. Web-based study information and consent to participate

Background and purpose	The aim of this study is to investigate physicians' management of a patient in a case vignette.
Request for participation	The study is aimed for doctors who meet and treat patients with respiratory problems and reduced physical capacity.
What does the study involve?	The study consists of a short web questionnaire that takes about 15 minutes to complete. It contains some general questions about your training and type of practice, a patient description and a few questions about how you would manage this patient. Participation is anonymous and study participants cannot be identified. You can only participate in the study once.
What are the risks?	The study is not expected to involve any risk of discomfort or negative impact on the participant. For questions or comments please contact the research team (details below).
Are there any benefits?	Participation in the study involves no benefits or compensation.
Data handling and privacy	Survey responses will be kept anonymous on a password-protected server so that participants cannot be identified. The information will only be used to answer the study questions. Your answers will not be released to any unauthorised person. Landstinget Blekinge is responsible for all personal data as part of the data protection Act (1998:204). The data are saved 10 years to allow verification of the study's findings. The results will be published in international scientific journals in an aggregated form so that individual participants cannot be identified.
How do I get information about the results of the study?	Participation is anonymous and the participants' survey responses cannot be identified or disclosed after participation. The results will be published in international scientific journals.
Insurance, compensation	The study involves no insurance or compensation.
Volontary	Participation in the study is completely voluntary, and the participant may at any time, without explanation, cancel the web questionnaire and further responses will not be saved.
Responsible	Study sponsor: Landstinget Blekinge Responsible investigator: Zainab Ahmadi, doctor and PhD student, Department of Medicine, Karlskrona hospital, Blekinge 371 85. Email: zai.ahmd@gmail.com; ph: 0455-73 76 23.
Consent form	By selecting "Participate in study" below, I give my informed consent to participate in the study. [Button: "participate in the study"]

We would be grateful if you could fill in the details below

ID

To be included in the study, you must:
• Be a registered physician
• Treat patients with respiratory problems and reduced physical capacity
• Be able to read and understand the case description in Swedish
• Not have deeper knowledge of the study's design or content
• Not have previously participated in the study

Inclusion criteria

- ☐ All are true
- ☐ All are **not** true

Age

Sex

- ☐ Male
- ☐ Female

Level of doctor [select the highest applicable]

- ☐ Senior specialist
- ☐ Specialist
- ☐ Resident
- ☐ Junior doctor

Present location of practice

- ☐ Primary health care
- ☐ Hospital
- ☐ Other

Specialty license(s) [select all that apply]

- ☐ Family medicine
- ☐ Internal medicine
- ☐ Respiratory medicine
- ☐ Palliative medicine
- ☐ Other

Specialty license [If other]

Current specialty area(s) of practice [select all that apply]

- ☐ Family medicine
- ☐ Internal medicine
- ☐ Respiratory medicine
- ☐ Palliative medicine
- ☐ Other

Present working in specialty [If other]

Total work experience as physician

[Button: "submit"]

APPENDIX 2. Case scenario and questions

Please read the following case scenario carefully and then respond to a number of questions about how you would assess and manage the patient. Medical assessments are complex. Several responses may be "correct" and give comparable results. We are not looking for what is considered right, but **how you would actually treat the patient in your daily clinical practice.**

The questions are single or multiple choice. You must answer all questions in order to move on. You cannot go back to previous pages. Please note! Do not use the browser's "Back button" to return, as the system could freeze.

A 59-year-old [man/woman] is consulting you with respiratory problems and reduced physical capacity. Smoked previously (in total 40 pack years) but stopped three years ago. Has been troubled for 4 years by morning cough and, at times, wheezing that worsens during respiratory infections. Has severe [breathlessness/pain]. Has been unable to ascend a flight of stairs or hills without stopping for the last 3 years. Is being treated for hypertension.

Current medications: T. Paracetamol 1 g x 4. T. Enalapril 20 mg x 1 and T. Metoprolol 100 mg x 1.

Allergy/hypersensitivity: NSAID (reaction to Diclofenac).

Status findings: Silent breath sounds bilaterally with scattered rhonchi. No edema. Body mass index (BMI) 20. No other findings.

What do you think is the most likely cause of the patient's respiratory problems and reduced physical capacity? (Please read all and then select the best match)

- ☐ Asthma
- ☐ Cancer
- ☐ Heart failure
- ☐ Chronic obstructive pulmonary disease (COPD)
- ☐ Chronic pulmonary emboli
- ☐ Other

Other [Please specify]

How do you investigate the cause of the patient's respiratory problems and reduced physical capacity? (select all relevant responses)

- ☐ Blood tests
- ☐ ECG
- ☐ Exercise ECG
- ☐ Cardiac ultrasound
- ☐ Methacholine Challenge Test
- ☐ Oxygen saturation test
- ☐ Spirometry
- ☐ Sputum culture
- ☐ Chest x-ray

☐ Chest CT

☐ Other

Other [Please specify]

Svara

[man/woman] – The information in the parenthesis means randomisation to either a case with man or woman.
[breathlessness/pain] – The information in the parenthesis means randomisation to either a case with breathlessness or pain.

[Previous case scenario and information]

New information

Saturation: 95% on room air at rest.

Blood tests: Essentially normal blood count, CRP, sodium, potassium, creatinine, D-dimer and pro-BNP.

ECG: Sinus rhythm, heart rate of 72 beats/min, essentially normal appearance.

Chest x-ray: Essentially normal.

Spirometry after bronchodilator: $FEV_1/FVC = 0.54$; $FEV_1 = 38\%$ of predicted.

A recent chest CT scan: Emphysema and vertebral compression fracture of benign appearance.

You diagnose chronic obstructive pulmonary disease (COPD). The patient receives information about the disease as well as vaccination against influenza and Pneumococcus.

What treatment/measures do you offer as your first choice? (Please read all and then select the best match)

- ☐ Dietician contact
- ☐ Short-acting bronchodilators (eg. Bricanyl or Atrovent)
- ☐ Long-acting anticholinergics (eg. Spiriva)
- ☐ Long-acting beta-2-agonist (e.g., Oxis or Serevent)
- ☐ Both long-acting anticholinergics and long-acting beta-2 agonist
- ☐ Inhaled corticosteroids (eg. Pulmicort)
- ☐ Triple therapy with long-acting anticholinergics and long-acting beta-2-agonist and inhaled corticosteroid
- ☐ Oral Steroid course
- ☐ Rehabilitation therapy
- ☐ Oxygen therapy

What further treatment options do you consider? (select all that you offer)

- ☐ Dietician contact
- ☐ Short-acting bronchodilators (eg. Bricanyl or Atrovent)
- ☐ Long-acting anticholinergics (eg. Spiriva)
- ☐ Long-acting beta-2-agonist (e.g., Oxis or Serevent)
- ☐ Both long-acting anticholinergics and long-acting beta-2 agonist
- ☐ Inhaled corticosteroids (eg. Pulmicort)
- ☐ Triple therapy with long-acting anticholinergics, long-acting beta-2-agonist and inhaled corticosteroid
- ☐ Oral Steroid course
- ☐ Rehabilitation training
- ☐ Oxygen therapy

[Previous case scenario and information]

New information

The patient returns to you for follow-up after three months. The patient is reporting substantially unchanged symptoms. Is troubled by severe breathlessness/pain that markedly restricts daily activities.
The patient is on triple therapy with inhalations of long-acting anticholinergics, long-acting beta-2-agonist and corticosteroids. He/She has received assistance with her inhalation technique and states that he/she taken the drugs as prescribed. The patient has also undergone 8 weeks of customized rehabilitation training with a physiotherapist.

How do you manage the patient now? (Please read all responses and then select the best match)

- ☐ Additional diagnostic measures
- ☐ Additional treatment
- ☐ Active watchful waiting with follow-up visit
- ☐ Has optimal treatment at present, new contact if necessary

[Previous case scenario and information]

[Only for participants who chose Additional treatment]

What do you want to treat additionally in the first place? (Please read all and then select the best match)

- ☐ The COPD
- ☐ Symptoms
- ☐ Other

Other [Please specify]

[Previous case scenario and information]

Which treatment do you offer as your first choice? (Please read all responses and then select the best match)

- ☐ Changed inhalational therapy
- ☐ Intensified rehabilitation training
- ☐ Benzodiazepines (tranquilizers)
- ☐ Opioid (e.g. morphine)
- ☐ Oral steroid cycle (e.g. prednisolone)
- ☐ Roflumilast (Daxas)
- ☐ Oxygen therapy
- ☐ Theophylline
- ☐ Other

Other [Please specify]

Which treatments are relevant? (select all that you offer)

- ☐ Changed inhalational therapy
- ☐ Intensified rehabilitation training
- ☐ Benzodiazepines (tranquilizers)
- ☐ Opioid (e.g. morphine)
- ☐ Oral steroid cycle (e.g. prednisolone)
- ☐ Roflumilast (Daxas)
- ☐ Oxygen therapy
- ☐ Theophylline
- ☐ Other

Other [Please specify]

[Previous case scenario and information]

The main reason for not treating the patient in the case with opioids (e.g. morphine) for [breathlessness/pain]? (Please read all responses and select the one that best describes)

- ☐ Chose to treat with an opioid
- ☐ This symptom often goes away by itself or does not need to be treated
- ☐ Usually achieves adequate relief with other treatments
- ☐ There is a lack of evidence for treatment benefit
- ☐ Insufficient treatment guidelines
- ☐ Experience that opioids have insufficient benefit
- ☐ Insufficient knowledge of use/dosage
- ☐ Only relevant in more advanced disease for end of life care
- ☐ Concerns expressed by the patient and/or family members
- ☐ Risk of addiction/substance abuse
- ☐ Risk of serious adverse events
- ☐ Other

Other [Please specify]

Other factors contributing to the decision not to treat with opioids in this case for [breathlessness/back pain]? (select all that apply)

- ☐ Chose to treat with an opioid
- ☐ This symptom often goes away by itself or does not need to be treated
- ☐ Usually achieves adequate relief with other treatments
- ☐ There is a lack of evidence for treatment benefit
- ☐ Inadequate treatment guidelines
- ☐ Previous experience that opioids have insufficient benefit
- ☐ Inadequate knowledge of use/dosage
- ☐ Only for use in more advanced disease or for end-of-life care
- ☐ Concerns expressed by the patient and/or family members
- ☐ Risk of addiction/substance abuse
- ☐ Risk of confusion
- ☐ Risk of injuries from falls
- ☐ Risk of impaired breathing/respiratory depression
- ☐ Risk of premature death
- ☐ Other

Other [Please specify]

[Previous case scenario and information]

New information

The patient is limited by breathlessness of an intensity 7 out of a maximum of 10

In your opinion, does the patient in the case have significant breathlessness despite optimal treatment for underlying cause(s) (chronic breathlessness)?

- ☐ Yes
- ☐ No

If no, please specify the reason why it's not chronic breathlessness? Please specify:

[Previous case scenario and information]

How strong do you consider the the scientific support to be for the following treatments for chronic breathlessness in severe COPD? (Note: This relates to the evidence base in general, not to this specific case)

Benzodiazepines

- ☐ None
- ☐ Low
- ☐ Moderate
- ☐ Strong scientific support

Changed inhalational therapy

- ☐ None
- ☐ Low
- ☐ Moderate
- ☐ Strong scientific support

Walking aid if necessary

- ☐ None
- ☐ Low
- ☐ Moderate
- ☐ Strong scientific support

Opioid (morphine)

- ☐ None
- ☐ Low
- ☐ Moderate
- ☐ Strong scientific support

Oral cortisone course

- ☐ None
- ☐ Low
- ☐ Moderate
- ☐ Strong scientific support

Rehabilitation training

- ☐ None
- ☐ Low
- ☐ Moderate
- ☐ Strong scientific support

Oxygen therapy

- [ ] None
- [ ] Low
- [ ] Moderate
- [ ] Strong scientific support

Other [Please specify]

Other

- [ ] None
- [ ] Low
- [ ] Moderate
- [ ] Strong scientific support

[Previous case scenario and information]

How often do you prescribe an opioid (e.g. morphine) for pain for patients with severe COPD?

- ☐ Never
- ☐ Very rarely (once per year)
- ☐ Sometimes (once a month)
- ☐ more often than monthly

[Previous case scenario and information]

How often do you prescribe an opioid (e.g. morphine) for breathlessness for patients with severe COPD?

- ☐ Never
- ☐ Very rarely (once per year)
- ☐ Sometimes (once in the month)
- ☐ More often than monthly

[Previous case scenario and information]

To what extent do you agree with the following statements?

Opioid therapy relieves chronic breathlessness

- ☐ Not at all
- ☐ A bit
- ☐ Moderate
- ☐ Very

Opioid therapy increases the risk of adverse events (hospitalization, respiratory depression or death)

- ☐ Not at all
- ☐ A bit
- ☐ Moderate
- ☐ Very

Opioid therapy causes more damage or more benefit in the treatment of chronic breathlessness?

- ☐ Much more damage
- ☐ A little more damage
- ☐ No difference
- ☐ A little more benefit
- ☐ Much more benefit

Printed by Media-Tryck, Lund 2019 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences
Respiratory Medicine and Allergology

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2019:58
ISBN 978-91-7619-787-5
ISSN 1652-8220