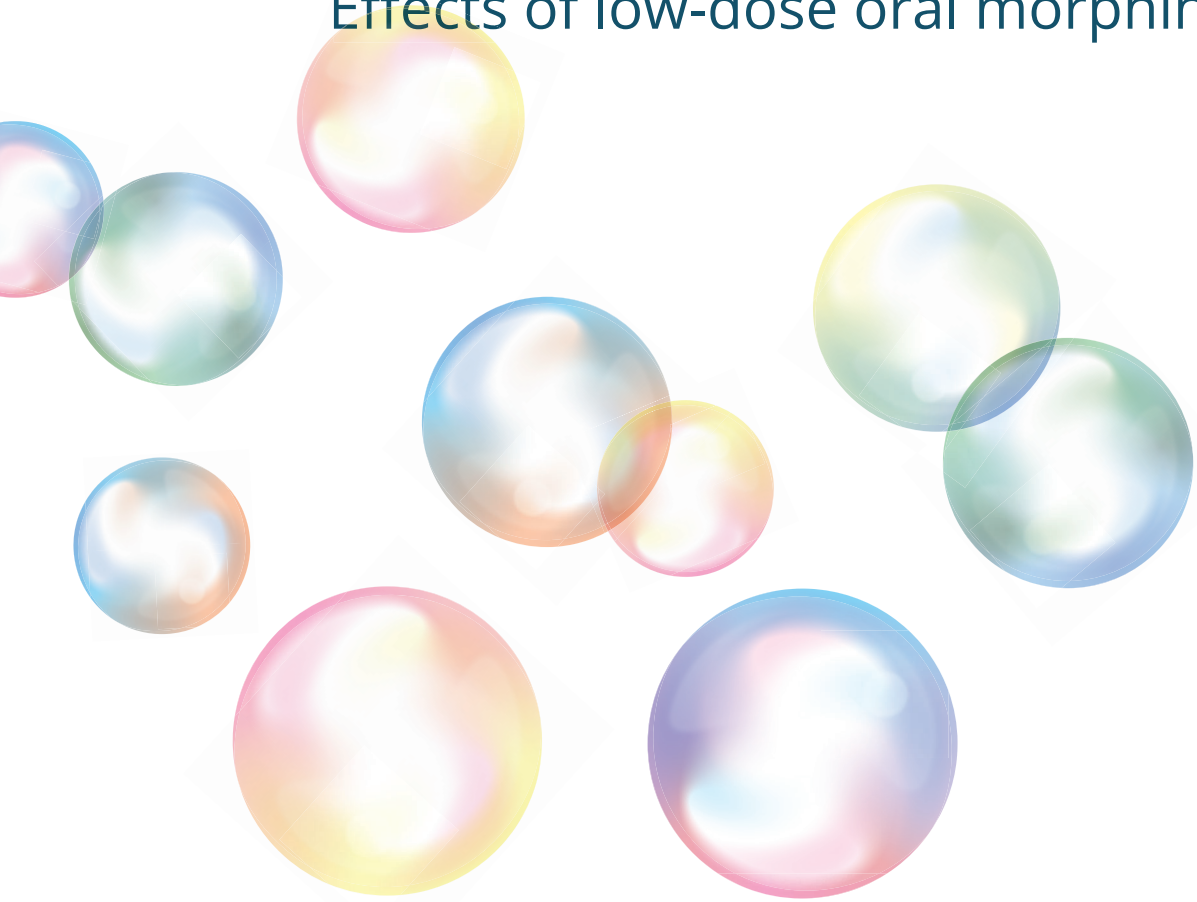
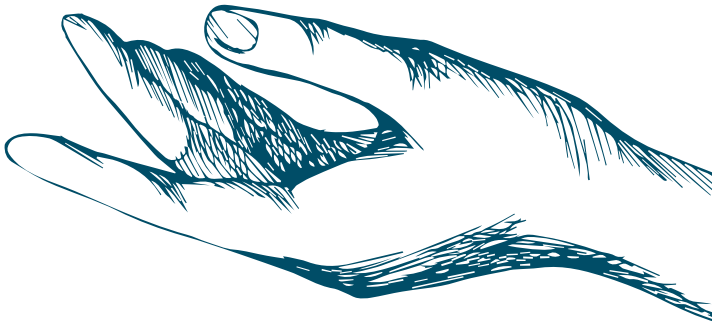
Chronic breathlessness in COPD

CHRONIC BREATHLESSNESS IN COPD

Effects of low-dose oral morphine





Cindy van den Berg - Verberkt

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The research presented in this thesis was conducted at CAPHRI Care and Public Health Research Institute, Department of Health Services Research, of Maastricht University. CAPHRI participates in the Netherlands School of Public Health and Care Research (CaRe). The research was conducted in close collaboration with Ciro, Horn and the center of expertise in palliative care of Maastricht UMC+. The research was funded by ZonMW.

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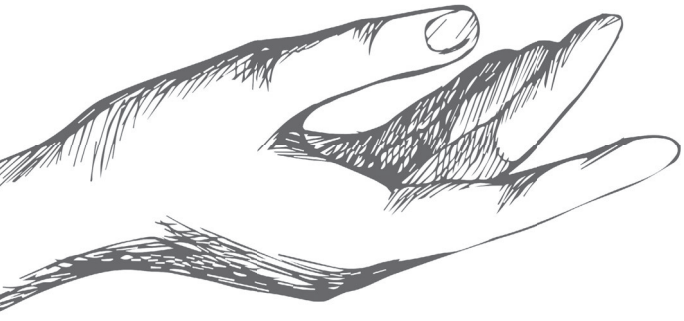

CHAPTER 1

General introduction

Chronic obstructive pulmonary disease (COPD)

COPD is defined as '*a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality'*.[1] Worldwide, the prevalence of COPD was estimated by the Global Burden of Disease Study at 3.9% in 2017.[2] COPD is a major cause of burden and mortality. Annually, COPD accounts for 5.7% of all-cause deaths and 3.3% of all-cause disability-adjusted life years.[2] In the Netherlands, the prevalence was estimated at 3.4% in 2019, and about 7000 people died because of COPD.[3] Due to longevity and persistent exposure to COPD risk factors, prevalence and burden of COPD will continue to increase.[1] According to the World Health Organization (WHO), COPD will be the fourth leading cause of mortality and the seventh leading cause of disability-adjusted life years in 2030.[4] COPD is also associated with an increased economic and societal burden. COPD results in increased disability, leading to increased healthcare costs. Within the European Union, 6% of healthcare spending is accounted to direct costs of COPD.[5] Especially exacerbations and hospital admissions attribute to an increase in healthcare costs.[6-9]

Most common symptoms in advanced COPD are breathlessness, fatigue, muscle weakness, cough and sputum production.[1,10] Presence of these symptoms has a major impact on quality of life and functional status.[11-13] A prospective survey among 100 patients with advanced COPD showed that impairment in quality of life was strongly associated with high symptom burden, disease-related dysfunction and impaired psychological wellbeing.[14] Furthermore, COPD is associated with a higher number of comorbidities than other diseases,[15] including cardiovascular, cachectic, metabolic and psychological comorbidities.[10,16] As was shown by a cross-sectional analysis of Scottish national data, half of patients with COPD aged over 65 has at least three other morbidities.[17]

Management of COPD includes reduction of exposure to risk factors like smoking cessation, pharmacological treatment like inhaled bronchodilators or corticosteroids and nonpharmacological treatment like pulmonary rehabilitation. In patients who still experience symptoms despite optimal pharmacological and nonpharmacological management, palliative care is indicated.[1]

Palliative care

Palliative care is defined by the WHO as '*an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and*

impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care provides relief from pain and other distressing symptoms; affirms life and regards dying as a normal process; intends neither to hasten or postpone death; integrates the psychological and spiritual aspects of patient care; offers a support system to help patients live as actively as possible until death; offers a support system to help the family cope during the patients illness and in their own bereavement; uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated; will enhance quality of life and may also positively influence the course of illness; is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy; and includes those investigations needed to better understand and manage distressing clinical complications.'[18] Palliative care is directed to relief of distressing symptoms, enhancement of quality of life and supporting loved ones during the palliative phase of the disease and after the patient is deceased. Palliative care can be provided simultaneously to disease-modifying treatment and is a multidisciplinary approach in which generalist and specialist caregivers collaborate with the patient and his or her loved ones, taking into account the values, wishes and needs of the patient.[19] Palliative care improves the patient's quality of life, symptom burden, healthcare utilization and patient and caregiver satisfaction after one to three months of follow-up, without affecting survival.[20]

Palliative care in patients with COPD

A large proportion of patients with COPD experience symptom burden despite optimal treatment of their disease and comorbidities.[10] There is a need for additional treatment, next to the disease-modifying treatment, to reduce symptoms and improve functioning and quality of life. Patients with advanced COPD more often experience worse quality of life and symptoms of anxiety, depression or breathlessness compared to patients with lung cancer.[21,22] However, patients with COPD are less likely to receive symptom relief in the last six months of life compared to patients with lung cancer.[23]

The course of COPD is unpredictable, with patients often living with the disease for years. They experience acute deteriorations, mainly due to exacerbations, and often there is no distinct terminal phase.[24,25] Therefore, early recognition of palliative care needs in COPD is important. This is also endorsed by pulmonologists.[26] During stable phases of the disease, patients in the Netherlands are treated by several different (para)medical specialists, like the general practitioner, pulmonologist, pulmonary nurse specialist or physiotherapist. During hospital admissions, treatment is mainly performed by pulmonologists (in training) and pulmonary nurse specialists.[26] Furthermore, due to comorbidities, other specialties are often involved as well. Therefore, a multidisciplinary and integrated management is necessary to provide the most optimal palliative care.[27]

Breathlessness

Breathlessness is one of the most common symptoms in advanced COPD and is reported by 94% of patients.[10] It is a multidimensional experience, and the underlying mechanisms are complex. Breathlessness is defined as '*a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity*'.[28] This breathing discomfort originates from an imbalance between the afferent information to the central nervous system and the mechanical response of the respiratory system, also called an efferent-afferent dissociation or demand-capacity imbalance.[29,30] Afferent sensory information from mechanoreceptors, chemoreceptors and respiratory muscle receptors throughout the respiratory system is processed in the central nervous system, specifically in respiratory control centers in the brainstem. Efferent output from the respiratory control centers to respiratory muscles controls respiration. Information on this output is relayed to the somatosensory cortex via corollary discharge.[29-31] In the somatosensory cortex, afferent input and efferent output is compared. A mismatch between input and output beyond a certain threshold is perceived as breathlessness, specifically the sensory component of breathlessness (i.e. intensity).[28-30] Afferent information is relayed to the limbic system as well. As this system is involved in the affective state, the efferent-afferent dissociation provokes a strong emotional response to breathlessness (i.e. anxiety, panic, distress), inducing the affective component of breathlessness (i.e. unpleasantness).[29,31,32] Perception of breathlessness is influenced by expectations and beliefs based on previous experiences (priors). This process of anticipatory learning evokes conditional behavioral (avoidance) responses.[30-32]

The language of breathlessness

The different mechanisms and afferent pathways involved in breathing are associated with distinct different sensory qualities.[28] These qualities can vary in intensity and unpleasantness,[28] can vary over the day or week[33] and are described by a variety of descriptors.[28] Patients with different medical conditions use different descriptors.[28,34,35] Also, different sensations can be induced in healthy volunteers using different physiological mechanisms.[28,36,37] These descriptors have been combined in factor analytic studies to clusters.[34,35] The cluster of breathing work/effort (*'I feel out of breath'* or *'my breathing requires work/effort'*) is hypothesized to originate from a mismatch between afferent input from respiratory muscle receptors and increased voluntary respiratory motor output. On the contrary, the cluster of air hunger/unsatisfied inspiration (*'I cannot get enough air'*) has been related to an increased spontaneous ventilatory drive, which cannot be fulfilled with sufficient ventilation. A third common cluster of sensory descriptors is chest tightness (*'my chest feels tight/constricted'*). This cluster is commonly related to bronchoconstriction and arises from stimulation of airway receptors. Where patients with COPD during stable phases of their disease usually describe their breathlessness as breathing

work/effort and air hunger, patients usually experience all clusters during an exacerbation.[34,35,38-40]

Assessing breathlessness

Measurement of breathlessness serves different purposes. *First*, measures can be used to discriminate between patients with mild or severe breathlessness. *Second*, change of breathlessness over time can be measured, for instance to evaluate the effectiveness of an intervention.[41]

Since breathlessness is a subjective sensation, it is assessed using patient-reported measures. Intensity of breathlessness is generally assessed with unidimensional measures like a visual analogue scale (VAS),[42] numeric rating scale (NRS)[43] or modified Borg scale.[44] Using these measures, breathlessness during a certain period (i.e. today, during the previous week) or during a certain activity (i.e. walking, climbing the stairs) can be assessed. These measures are especially suited to evaluate changes of breathlessness over time and less useful to discriminate between patients.[45] The minimal clinical important difference of the 0-100 VAS and 0-10 NRS has been determined at 10 points or 1 point, respectively.[46]

Burden or impact of breathlessness on daily activities is most frequently assessed using the modified Medical Research Council (mMRC) breathlessness scale.[47,48] The mMRC breathlessness scale is a short and simple assessment, including five descriptions of impact of breathlessness on functional ability: grade 0 (*'I only get breathless with strenuous exercise'*) to grade 4 (*'I am too breathless to leave the house or I am breathless when dressing'*). The mMRC is able to discriminate between patients with low breathlessness burden (mMRC grade 0 to 1) and patients with high breathlessness burden (mMRC grade ≥2).[1] Also, the mMRC has shown to predict survival in patients with COPD.[49,50] Due to the broad grades the mMRC has limited ability to assess changes over time.[51]

Finally, the multidimensional properties of breathlessness can be assessed using measures like the Multidimensional Dyspnea Profile.[52,53] The Multidimensional Dyspnea Profile assesses both the sensory and affective dimensions of breathlessness. Breathing unpleasantness, five sensory clusters (breathing work/effort, air hunger, chest tightness, mental effort and hyperpnoea) and five affective emotional responses (depression, anxiety, frustration, anger and fear) are rated on a 0 to 10 NRS. This measure has shown to be responsive to clinical changes over time.[53]

Breathlessness burden

Breathlessness can be an invisible symptom for the patient's environment and healthcare professionals,[54] but has major psychosocial consequences like care dependency, social limitations and anxiety.[13] When COPD progresses and breathlessness worsens, patients experience more trouble during daily life activities, more anxiety restricting them to their house and growing dependence. This shifts over time with ups and downs due to the erratic course of COPD.[54]

Worsening of breathlessness over time increases healthcare utilization.[8,9] Patients with high breathlessness burden (mMRC grade ≥2) have more inpatients and outpatient healthcare utilization compared to patients with low breathlessness burden during a period of six months. These patients also receive more prescriptions for COPD-related medication.[9] Main cost drivers are exacerbations and hospital admissions.[8,9] Furthermore, healthcare utilization increases with the presence of comorbidities.[6] The worsening of breathlessness over time impacts workplace productivity and activities of daily living, leading to an increasing need for help from informal caregivers.[8,55,56] Societal costs increase significant when an informal caregiver is involved.[8] Costs for lost productivity are mainly driven by early retirement of patients.[55] This emphasizes the societal burden of COPD. As the current knowledge on the economic burden of breathlessness arises from studies using retrospective claims data, the long-term impact of breathlessness on healthcare and societal costs as reported by patients is not known.

Treatment of breathlessness

Breathlessness can be insensitive to treatment of the underlying disease and result in disability, thus becoming a treatment goal in itself.[57] Current clinical guidelines emphasize the importance of palliation of chronic breathlessness using (a combination of) pharmacological and nonpharmacological interventions.[58,59]

Pulmonary rehabilitation has shown to be an effective intervention to improve breathlessness, exercise capacity and quality of life.[60] A pulmonary rehabilitation program should ideally last six to eight weeks and should be personalized.[1] Components of pulmonary rehabilitation include education, self-management, endurance and strength training (including neuromuscular electrical stimulation and inspiratory muscle training), breathing strategies and the opportunity for nutritional support, smoking cessation and psychosocial support.[61] Use of a hand-held fan directed to the face has shown to decrease breathlessness when used for at least five minutes.[62,63] The main perceived benefit was a shorter recovery time after activity.[64] Other nonpharmacological treatment interventions include the use of walking aids (i.e. walker),[65] breathing techniques,[66,67] inspiratory and expiratory muscle training,[68,69] long-term oxygen therapy for patient with severe hypoxemia[70] and noninvasive ventilation for patients with hypercapnia.[71,72]

Pharmacological interventions include opioids, benzodiazepines and antidepressants. Opioids will be discussed in the next section. Benzodiazepines relieve anxiety and are used to treat breathlessness. However, a Cochrane review showed that benzodiazepines have no beneficial effect on breathlessness, both for the total included population of 214 patients with chronic breathlessness as for the subpopulation of 61 patients with COPD. There was no difference in type of benzodiazepine, dose, route or dosing schedule. Patients in the treatment group had an increased risk of adverse effects.[73] Recently, two randomized controlled trials have assessed the effect of antidepressants on breathlessness. Sertraline

did not show a beneficial effect after four weeks in 223 patients with chronic breathlessness.[74] The same results were found for mirtazapine treatment after four weeks in 64 patients with chronic breathlessness.[75]

Opioids

It has been hypothesized that opioids relieve breathlessness by centrally modulating the perception of breathlessness.[76] Opioids modulate the awareness of breathlessness by acting upon respiratory control centers and centers in the somatosensory cortex involved in respiration.[77-79]
Also, in processing afferent sensory information in the central nervous system, limbic areas (including the anterior cingulate cortex, amygdala and thalamus) are activated.[29,32] As these areas are abundantly innervated with opioid receptors, they are involved in modulation of breathlessness by opioids as well.[80,81] The most extensively studied opioid to treat chronic breathlessness is morphine.

Effectiveness
Several systematic reviews have determined the effect of opioids for chronic breathlessness.[82-85] The first Cochrane systematic review, conducted in patients with different life-limiting illnesses,[82] showed moderate-level evidence that oral and parenteral opioids significantly reduced breathlessness, while nebulized opioids did not. A subgroup analysis in patients with COPD showed similar results as in the total included population. An update of this systematic review in 2016 showed smaller effects.[83] However, the meta-analysis, which did not account for cross-over designs and a repeat analysis,[85] showed a mean difference of 1 point on a 0 to 10 NRS, which corresponds to a clinically important difference.[86] A third systematic review was performed in patients with COPD and showed moderate-level evidence that opioids improved breathlessness. The evidence was most consistent for systemic opioids and when given in steady state.[84]
As the goal of palliative care is to improve quality of life, among other things, by alleviating symptoms,[18] it is important to assess the effect of palliative treatment on quality of life. Only five studies so far have included an outcome of quality of life, of which three showed no effect.[87-89] Shohrati et al.[90] showed an improvement of global quality of life after five days of nebulized morphine. Poole et al.[91] reported a slight worsening of the mastery domain of the Chronic Respiratory Disease Questionnaire after six weeks of sustained-release morphine.
The effect of opioids on functional performance has been studied more extensively. Three meta-analyses showed no effect of opioids on exercise performance.[82-84] The results were consistent for systemic and nebulized opioids and for measurements at steady state. A recent small clinical trial on the acute effect of a single dose of immediate-release morphine during constant-load cardiopulmonary cycle

exercise testing showed that exertional breathlessness and exercise endurance improved significantly and clinically relevant. This improvement was associated with a reduction in ventilation and respiratory rate.[78] Since the vast majority of studies examined the effect on functional performance after a single dose or a short treatment duration, the long-term effect of opioids on functional performance remains unknown.

Safety and adverse effects

As opioids have been an important analgesic treatment for centuries, the safety and occurrence of adverse effects has been studied extensively. In fear of the occurrence of respiratory depression or other adverse effects, physicians indicate to be hesitant to prescribe opioids to patients with advanced COPD.[92-94] Systematic reviews on the effects of opioids on chronic breathlessness showed no evidence for an effect of opioids on respiratory outcomes.[82-84] On the contrary, three case reports have described cases of serious respiratory depression after high doses of nebulized morphine,[95] immediate-release oral morphine[96] or transmucosal fentanyl.[97] Known other adverse effects of morphine are nausea, constipation and drowsiness. Clinical studies into the treatment of chronic breathlessness have shown that these adverse effects are mainly mild or moderate. Symptoms reduce after treatment with laxatives or anti-emetics or resolve after discontinuation of the treatment. No serious adverse effects have been registered.[82-84,98]

Safety profiles on the longer term have been assessed in large observational studies. A prospective cohort of 2249 patients with COPD starting long-term oxygen therapy that was followed-up for four years showed no increase in hospital admissions or increased mortality after treatment with ≤30 mg morphine equivalent per day.[99] A retrospective cohort of 130,979 patients with COPD showed that the incidence of opioid prescription was 68.2% and was associated with a small increase in respiratory-related hospital admissions, respiratory-related mortality and all-cause mortality within 30 days after commencement of the treatment.[100] However, the opioid dose or indication of prescription was unknown.

Beneficial response to morphine

A dose increment and pharmacovigilance study in patients with different life-limiting illnesses has been performed.[101,102] Patient started at 10 mg sustained-release morphine per day for one week. When no clinical relevant improvement was shown after this week, the dose was increased to 20 mg per day for a week and necessarily to 30 mg per day a week later. Results showed that 62% of patients accomplished a clinically relevant improvement in breathlessness. For 70% of these patients, 10 mg per day was effective.[101] In patients that needed upward titration to 20 or 30 mg daily, an improvement was shown within the first 24 hours. The effect continued to improve over the successive six days.[102] Patients that showed a clinically relevant

improvement were followed-up; about one-third of patients maintained benefit after three months of treatment.[101]
The above mentioned study also shows that 31% of patients showed no beneficial effect to morphine at the maximal dose or experienced unacceptable side effects and withdrew before achieving the maximal dose. Current literature is conflicting regarding whether breathlessness intensity, age and clusters of sensory description of breathlessness are predictors of response to morphine.[101,103,104] Younger age has been associated with a beneficial response.[103,104] Worse baseline breathlessness intensity was not associated with a beneficial response in two clinical trials,[101,103] but a pooled analysis did show a favorable effect.[104] Results on the contribution of clusters of sensory breathlessness description suggest a favorable effect in laboratory models in healthy subject describing breathlessness as air hunger,[105] but not as breathing work/effort.[106] In a mixed patient population, a favorable effect for air hunger was shown as well.[104] However, since patients with different conditions use different descriptors,[34-36] it remains unknown what the attribution of sensory description of breathlessness on a beneficial response to morphine in COPD is.

Attitudes of physicians and patients
Although opioids have proven to be effective and safe and are recommended in several national and international guidelines, chronic breathlessness is often still undertreated.[107,108] Although physicians recognize chronic breathlessness in a case scenario, they are less likely to recognize the need for further treatment and offer symptomatic treatment, and are less likely to prescribe opioids compared to patients with chronic pain.[109] In daily practice, 47% of physicians,[109] 45% of general practitioners,[110] 18.5% of pulmonologists[92] and 13.5% of junior doctors[111] report not to prescribe opioids to outpatients with advanced COPD. Main reasons for not treating with opioids mentioned by physicians are insufficient knowledge or experience, risk of adverse effects, including respiratory depression, resistance of the patient and lack of guidelines.[92-94,109-111]
Small qualitative studies in patients revealed barriers like fear of dependence and fear of imminent death.[93,112] Clinical studies on the effect of opioids had difficulties including patients.[98,113] Patients that did start opioid treatment mentioned doing as much as possible as most important reason.[93,112]

Aims of this thesis

Chronic breathlessness is a common and significant symptom in patients with advanced COPD. Opioids are suggested as palliative treatment, with the best evidence for low-dose, oral sustained-relief morphine. Palliative care is directed at relief of distressing symptoms and enhancing quality of life, without hastening death. Not all of these aspects are clear for low-dose morphine. The effect on quality

of life, functional performance, respiratory outcomes and breathlessness remains conflicting. Also, the long-term economic burden of chronic breathlessness using prospective, patient-reported data is unclear and no data on cost-effectiveness of oral morphine treatment is available. Therefore, the central aim of this thesis was to assess these palliative aspects of low-dose morphine.

The specific aims of this thesis were:

- To systematically review the occurrence of respiratory adverse effects in patients with life-limiting illnesses and chronic breathlessness who are treated with opioids;
- To examine whether and to what extent regular, low-dose, oral sustained-release morphine leads to respiratory adverse effects in patients with advanced COPD and chronic breathlessness;
- To study whether and to what extent regular, low-dose, oral sustained-release morphine improves disease-specific health status, functional performance and breathlessness in patients with advanced COPD and chronic breathlessness;
- To explore the relationship between response to morphine, intensity and sensory description of breathlessness and baseline characteristics in patients with advanced COPD and chronic breathlessness;
- To analyze the impact of breathlessness burden in COPD on healthcare and societal costs;
- To analyze the cost-effectiveness of regular, low-dose, oral sustained-release morphine in patients with advanced COPD and chronic breathlessness from a healthcare and societal perspective;
- To assess the willingness of patients with chronic lung disease or chronic heart failure to use opioids for chronic breathlessness and possible barriers or reasons to use opioids.

Outline

Chapter 2 describes the results of a systematic review and meta-analysis, which examines the effect of opioid treatment for chronic breathlessness on respiratory outcomes in patients with life-limiting illnesses. **Chapter 3** presents the economic burden of chronic breathlessness. This chapter describes the healthcare and societal costs during a two-year follow-up in patients with COPD who recently completed a comprehensive pulmonary rehabilitation program. **Chapter 4** describes the methodology of a randomized, double-blind, placebo-controlled, parallel-arm intervention study we performed for this thesis in detail. **Chapter 5** presents the clinical results of this randomized clinical trial. More specifically, it shows the effect of regular, low-dose, oral sustained-release morphine on health-related quality of life, respiratory outcomes, breathlessness and functional performance. **Chapter**

6 shows the relationship between a beneficial response to regular, low-dose, oral morphine treatment, intensity and description of breathlessness and baseline patient characteristics. **Chapter 7** describes the cost-effectiveness of regular, low-dose, oral sustained-release morphine treatment from a healthcare and societal perspective. **Chapter 8** explores the willingness of patients with chronic lung or heart disease to use opioids for breathlessness and perceived barriers or reasons to use opioids. **Chapter 9** is the general discussion, in which the clinical implications of this thesis and directions for future research are discussed.

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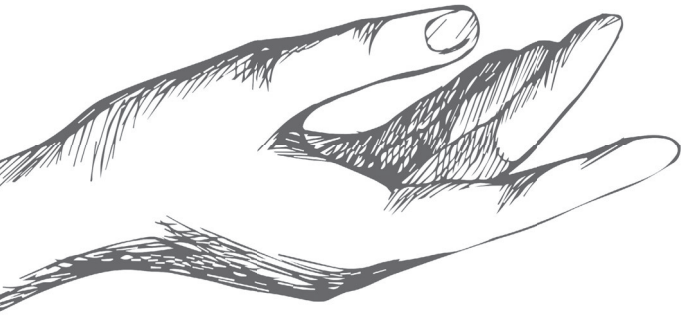

CHAPTER 2

Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis

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Abstract

Previous studies have shown that opioids can reduce chronic breathlessness in advanced disease. However, physicians remain reluctant to prescribe opioids for these patients, commonly due to fear of respiratory adverse effects. The aim of this study was to systematically review reported respiratory adverse effects of opioids in patients with advanced disease and chronic breathlessness.

PubMed, Embase, the Cochrane Central Register of Controlled Trials, CINAHL, ClinicalTrials.gov and the reference lists of relevant systematic reviews were searched. Two independent researchers screened against predefined inclusion criteria and extracted data. Meta-analysis was conducted where possible.

We included 63 out of 1990 articles, describing 67 studies. Meta-analysis showed an increase in carbon dioxide tension (0.27 kPa, 95% CI 0.08 to 0.45 kPa) and no significant change in oxygen tension and oxygen saturation (both $p>0.05$). Nonserious respiratory depression (definition variable/not stated) was described in four out of 1064 patients. One cancer patient pretreated with morphine for pain needed temporary respiratory support following nebulised morphine for breathlessness (single case study).

We found no evidence of significant or clinically relevant respiratory adverse effects of opioids for chronic breathlessness. Heterogeneity of design and study population, and low study quality are limitations. Larger studies designed to detect respiratory adverse effects are needed.

Take home message
There is no evidence for clinically relevant respiratory adverse effects of opioids for chronic breathlessness.

Introduction

Breathlessness is defined as *'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'*.[1] Breathlessness is one of the most uncomfortable symptoms in patients with advanced disease.[1] In cancer, 50 to 70% of patients suffer from breathlessness, while in chronic obstructive pulmonary disease (COPD) this prevalence is as much as 56 to 98%.[2,3]

Opioids can reduce chronic breathlessness (breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability[4]) in patients with advanced diseases.[5-8] However, while physicians are mostly willing to prescribe opioids for breathlessness in the last days or weeks of life, they are often reluctant to prescribe opioids to those earlier in their disease trajectory.[9] Their main concerns are fears of respiratory adverse effects and lack of evidence-based guidelines.[10-12] Data about respiratory adverse effects of opioids are limited and conflicting. Systematic reviews on the effects of opioids on chronic breathlessness in adults with advanced life-limiting disease showed no evidence for the following outcomes: respiratory depression, increase in arterial carbon dioxide tension ($PaCO_2$), increase in end-tidal carbon dioxide tension ($P_{ET}CO_2$), decrease in arterial oxygen tension (PaO_2) or decrease in arterial oxygen saturation (SaO_2).[5-8] However, meta-analyses on these outcomes have not been conducted before.

Conversely, observational studies have reported one or more cases of severe respiratory depression in patients using opioids for breathlessness.[13-16] Most guidelines in palliative care recommend the use of opioids for chronic breathlessness.[17-19] However, guidelines in respiratory medicine, for example the recent Global Initiative for Chronic Obstructive Lung Disease guidelines,[20] are more circumspect because of possible serious adverse events and limited effectiveness. To date there is little evidence whether and to what extent opioids lead to respiratory adverse effects in patients with chronic breathlessness.

The aim of this systematic review and meta-analysis was to study the occurrence of respiratory adverse effects (in particular increase of $PaCO_2$ and $P_{ET}CO_2$, decrease of PaO_2 and SaO_2, decrease in respiratory rate and occurrence of respiratory depression) in patients with advanced disease and chronic breathlessness who are treated with opioids. Respiratory adverse effects are examined in experimental studies and observational studies, as well as case reports. However, none of the previous reported reviews included all these study types. Therefore, to generate a full overview of the current knowledge, we included experimental studies, observational studies and case reports.

Methods

A systematic review and meta-analysis was performed according to the Cochrane methodology.[21] Results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[22] The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42016033691).

Search strategy

The following databases were searched: PubMed, Embase on Ovid, Cochrane Central Register of Controlled Trials and CINAHL on EBSCO (inception date to March 31, 2016). Search terms comprised (dyspnoea OR synonyms) AND (opioid OR synonyms) and included both terms of controlled vocabulary and free search in title and abstract (Supplemental Methods A-D). Furthermore, ClinicalTrials.gov was searched for ongoing or completed studies using the same search terms (May 29, 2017; Supplemental Methods E). Following de-duplication, we included all original research articles such as randomised controlled trials (RCTs), nonrandomised trials (NRTs), case-control studies, cohort studies, chart reviews, case reports and case studies. Reference lists of three relevant systematic reviews[6-8] were searched by hand and experts in the field were contacted. We included articles in the English, Dutch, German, French and Spanish languages. When a full-text article was not accessible, this was requested from the authors.

Study selection

For study screening, we used Endnote X7 (Thomson Reuters, Philadelphia, PA, USA). The titles and abstracts were screened independently by two researchers (CV and either DJ, MvdB or SD) and selected based on the description of treatment for chronic breathlessness using opioids. The remaining full-text articles were screened by two researchers (CV and either SD [English], DJ [German or Dutch] or LV [French or Spanish]) against all eligibility criteria: 1) participants included patients, regardless of their primary condition; 2) any opioid as intervention prescribed for breathlessness, regardless of dose or route of prescription; and 3) primary or secondary outcomes included $PaCO_2$, PaO_2, SaO_2 or respiratory rate. During the screening process, we decided in addition to include $P_{ET}CO_2$, occurrence of respiratory depression and breathlessness as outcomes. Any type of control group was considered. We excluded studies including only healthy subjects or studies that used an opioid in combination with other treatments and the effect of the opioid could not be distinguished. Consensus was reached by discussion. The study designs of included articles were categorised as follows: RCTs, NRTs, prospective observational studies (POSs), retrospective observational studies (ROSs) and case reports.

Risk of bias

Two researchers independently assessed the risk of bias on the study level (CV and either SD [English], DJ [German] or LV [French]). For the RCTs, we assessed this risk of bias regarding random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting using the Cochrane risk of bias tool.[21] In addition, the Cochrane risk of bias tool was used to assess the risk of bias in NRTs. Since no control condition was included in these studies, a high risk of selection bias, performance bias and detection bias were estimated in all NRTs. For POSs, we assessed the risk of bias regarding selection, comparability and exposure/outcome using the Newcastle-Ottawa quality assessment scale.[23] Consensus was reached by discussion. The risk of bias in ROSs and case reports was not assessed.

Data collection

Data were extracted by two researchers (CV and either SD [English], DJ [German] or LV [French]) using a predefined extraction form in Excel (Microsoft, Redmond, WA, USA), including data on study characteristics (design, duration, setting and inclusion and exclusion criteria), type of intervention (intervention, comparison, dose, mode and timing of administration), study population (sample size, age, sex, diagnosis, disease severity and use of oxygen) and outcomes (breathlessness, respiratory outcomes: $PaCO_2$, $P_{ET}CO_2$, PaO_2, SaO_2, respiratory rate and occurrence of respiratory depression, mode of assessment and missing data). When two articles appeared to describe overlapping research questions and study populations, we contacted the authors to request more information. We recorded the baseline values and change from baseline or post-treatment scores of the respiratory outcomes. When only a description of the change from baseline was given, this was taken into account. The form was piloted on two articles of each study type and adapted as needed.

Data synthesis

Change from baseline measurement scores or post-treatment measurement scores were collected for the $PaCO_2$, $P_{ET}CO_2$, PaO_2, SaO_2 and respiratory rate. For the RCTs, these results were compared between the intervention and control groups. For the NRTs, POSs, ROSs and case reports, the change from baseline was examined. Meta-analyses were performed using the results of RCTs; however, RCTs without a placebo comparator group were not included. When both a change from baseline and a post-treatment score were reported, the post-treatment score was used in the meta-analysis. Furthermore, the highest dose or latest measurement was included in the meta-analyses if multiple doses of the same opioid or repeated measurements were reported. When an RCT compared more than one opioid with placebo, the morphine group was included in the meta-analysis. For measurements on exertion, the submaximal measures at a fixed time point were included. To verify whether the included RCTs showed a pooled effect of improving breathlessness, meta-analysis on the effect of opioids on breathlessness was performed. These

results were presented as standardised mean difference (95% CI), since different scales to measure breathlessness were used. Results of the meta-analyses on $PaCO_2$, $P_{ET}CO_2$, PaO_2, SaO_2 and respiratory rate were presented as mean difference (MD) (95% CI), as the same scales to measure comparable outcomes were used. In all meta-analyses a random effects model was used, since the study designs were heterogeneous.[21] Results of PaO_2 and $PaCO_2$ that were reported in mmHg were converted to kPa (1 mmHg = 0.133 kPa).

Some RCTs contributed more than one contrast between the opioid and control group for the same outcome (i.e. subjects were measured multiple times under comparable conditions). To account for this clustering of multiple contrasts within one study sample, we used a multilevel meta-analysis approach to determine if any within-study clustering was present. If there was evidence of within-study clustering, quantified by the intraclass correlation coefficient, the results of the multilevel approach were preferred over the standard approach.[24] To examine the impact of the context of assessment (at rest or on exertion), the number of doses (single dose or multiple doses) or the route of administration (nebulised or systemic), a mixed-effects meta-regression was performed. Subgroup analyses were performed for variables which appeared to be of impact. When no impact appeared, all outcomes were analysed together.

When a study assessed the occurrence of respiratory depression, the frequency of occurrence and the definition used was reported. Analysis of this outcome was descriptive.

Analyses were performed using Review Manager (version 5.3; The Northern Cochrane Centre, 2014, Copenhagen, Denmark) and R (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria). GRADEPro Guideline Development Tool software (www.gradepro.org) was used to construct the Summary of Findings Table. Results are shown per category of respiratory adverse effect. p-values ≤0.05 were considered statistically significant.

Results

Study characteristics

The search identified 1990 articles, of which 63 met the inclusion criteria (Figure 1). The 63 articles included reported on 67 studies: 35 RCTs (Table 1), 17 NRTs (Table 1), four POSs (Supplemental Table S1), five ROSs (Supplemental Table S1) and six case reports (Supplemental Table S2). Six ongoing studies, four RCTs and two NRTs were identified (Supplemental Table S3). $PaCO_2$, PaO_2 and $P_{ET}CO_2$ were examined in one study; SaO_2 was examined in four studies and respiratory rate was examined in three studies. In one study, it is not clear which blood gases were examined. In one study the respiratory adverse effects were a primary outcome, and in five studies the respiratory adverse effects were secondary outcomes.

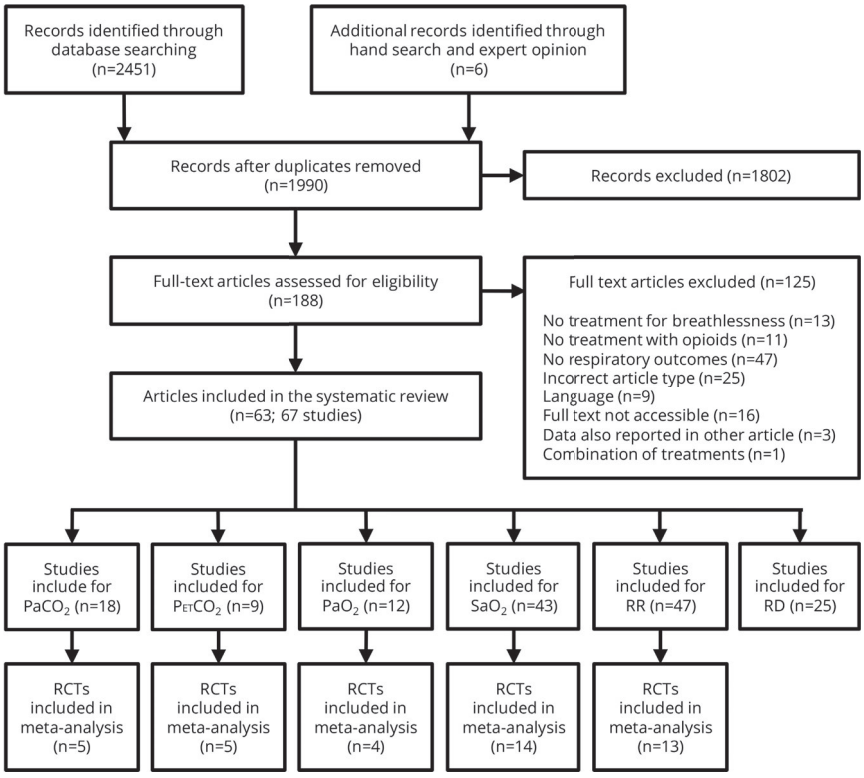

Figure 1. Study selection.
Abbreviations: $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; $P_{ET}CO_2$, end-tidal carbon dioxide tension; RCTs, randomised controlled trials; RD, respiratory depressions; RR, respiratory rate; SaO_2, arterial oxygen saturation.

19 RCTs were included in the meta-analysis on the effect of opioid treatment on breathlessness.[25-42] Eight RCTs used a visual analogue scale to examine breathlessness,[25,26,29,35,36,38,40] six RCTs used the Borg scale,[27,30-34] three RCTs used a numeric rating scale,[28,39,41] one RCT used the dyspnoea domain of the Chronic Respiratory Questionnaire[42] and one RCT used an oxygen cost diagram.[37] The RCTs that reported post-treatment scores showed effectivity of opioids in relieving breathlessness (standardised mean difference −0.42, 95% CI −0.62 to −0.21; I^2 27%; Supplemental Figure S1). The RCTs that reported changes from baseline were not able to show effectivity of opioids in relieving breathlessness (standardised mean difference −0.09, 95% CI −0.78 to 0.60; I^2 62%; Supplemental Figure S1).

Risk of bias

As shown in Supplemental Table S4, the risk of bias of the RCTs was estimated to be low or unclear in most studies. Other sources of bias were assessed as high risk in

43% of the studies, mainly because of the absence of a washout period in crossover trials. Supplemental Table S5 shows the risk of bias of the NRTs. High risk of selection bias, performance bias and detection bias were estimated, as no control condition was included in these studies. In the other categories, the risk of bias was assessed as low in most studies. The POSs were graded with three to six out of eight stars due to comparability and representativeness of cohorts (Supplemental Table S6).

Effect on outcomes of respiratory adverse effects

The effects of opioid treatment on outcomes of respiratory adverse effects are shown in Supplemental Tables S1, S2, S7 and S8. A summary of the effects of the RCTs included in the meta-analyses is presented in Table 2. Since none of the intraclass correlation coefficients of comparisons within RCTs were significantly different from zero, and therefore the effect of clustering on the outcomes was negligible for RCTs that contributed more than one contrast for a single outcome measure, the results are analyzed using regular meta-analyses instead of three-level meta-analyses. Most of the included RCTs were crossover trials, and we included both parallel and crossover trials in the meta-analyses together. Results of 12 RCTs could not be included in the meta-analyses because they compared opioid treatment to something other than placebo (treatment with another substance,[43-45] another dose or route of administration[46-49] or usual care[50] [Supplemental Table S7]). Results of seven RCTs could not be included in the meta-analyses because they reported their outcomes as median scores,[51] did not report the outcomes per treatment arm[52,53] or reported the outcome in qualitative wording only[30,54-56] (Supplemental Table S7).

Effect on $PaCO_2$

The effect of opioid treatment on $PaCO_2$ was assessed in nine RCTs,[29,33,37,43,45,50,51,55] five of which could be included in the meta-analysis.[29,33,37,51] The meta-analysis showed that treatment with opioids increased $PaCO_2$ (MD 0.27, 95% CI 0.08 to 0.45; I^2 0%; Figure 2a). The meta-regression revealed no influence from the context of assessment (p=0.437; however, there was only one RCT during exercise) or the number of doses (p=0.507) on the $PaCO_2$. Route of administration was not taken into account, since all RCTs administered the opioid systemically. One RCT examined the effect of opioids on $PaCO_2$ during exercise.[33] The difference between the intervention and control groups after administration of morphine was statistically significant at maximal exercise (5.8 and 5.1 kPa, respectively; p<0.001).

The effect on $PaCO_2$ was assessed in seven NRTs.[43,57-62] One NRT found a significant increase in $PaCO_2$.[57] Finally, the effect on $PaCO_2$ was assessed in one ROS[63] and one case report describing two cases.[64] In both studies the opioids were nebulised. The opioids were prescribed as a single dose or for up to 15 days. In all studies, $PaCO_2$ was measured at rest. None of these studies showed a significant effect of opioid treatment on $PaCO_2$.

Table 1. Patient characteristics, study design and included outcomes of included randomized controlled trials and nonrandomized trials

First author, year	Design	Subjects n (% male)	Population (n)	Age years	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
Abernethy, 2003[25]	Crossover	48 (73)	COPD (42) Cancer (3) MND (1) RLD (2)	76±5	Morphine SR	20 mg·day^{-1}	Oral	Placebo	4 days	Outpatient	SaO_2, RR, RD
Allard, 1999[46]	Parallel	33 (42)	Cancer (33)	63.3	Based on current treatment[a]	50% of current dose[a]	Oral or parenteral	25% of current dose[a]	Single dose	Inpatient	RR
Beauford, 1993[54]	Crossover	8 (88)	COPD (8)	60.8±9.1	Morphine	1, 4 or 10 mg	Nebulized	Placebo	Single dose	Outpatient	$P_{ET}CO_2$
Bruera, 1993 (part 1)[26]	Crossover	10	Cancer (10)	No data	Morphine	Target: 150% of current dose (34±12 mg)	Parenteral	Placebo	Single dose	Inpatient	SaO_2, RR
Charles, 2008[38]	Crossover	20 (55)	Cancer (20)	69 (range 48-83)	Hydromorphone[a,b]	5 mg	Nebulized	Placebo[b]	Single dose	Inpatient/ outpatient	SaO_2, RR
Chua, 1997[27]	Crossover	12 (100)	CHF (12)	65.5±1.5	Dihydrocodeine	1 mg·kg^{-1} body weight (77.4±3.1 kg)	Oral	Placebo	Single dose	Unclear	$P_{ET}CO_2$, SaO_2, RR
Cuervo Pinna, 2015[28]	Crossover	13 (85)	Cancer (13)	65.2±10.4	Fentanyl	Opioid-naïve: 200 µg Pretreated: 400 µg	Oral	Placebo	Single dose	Unclear	SaO_2, RR
Eiser, 1991 (part 1)[29]	Crossover	14 (57)	COPD (14)	65 (range 49-79)	Diamorphine	10 or 20 mg·day^{-1}	Oral	Placebo	2 weeks	Outpatient	$PaCO_2$, $P_{ET}CO_2$, PaO_2, SaO_2
Eiser, 1991 (part 2)[29]	Crossover	10 (60)	COPD (10)	65 (range 49-79)	Diamorphine	15 mg·day^{-1}	Oral	Placebo	1 day	Outpatient	$PaCO_2$, PaO_2
Gamborg, 2013[47]	Parallel	20 (10)	Cancer (20)	Median 69 (range 42-84)	Morphine	Target: 1/12 of total daily dose with a maximum of 24 mg (median 8.2%)	Oral	Subcutaneous morphine; 60% of 1/12 of total daily dose with a maximum of 14.4 mg	Single dose	Inpatient	SaO_2, RR, RD
Grimbert, 2004[52]	Crossover	12 (92)	Cancer (12)	63 (range 44-82)	Morphine	120 mg·day^{-1}	Nebulized	Placebo	2 days	Inpatient	SaO_2, RR

Table 1. Continued

First author, year	Design	Subjects n (% male)	Population (n)	Age years	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
Harris-Eze, 1995[30]	Crossover	6 (83)	ILD (6)	49±16	Morphine	Target: 2.5 mg (mean 1.9 mg) or 5 mg (mean 3.7 mg)	Nebulized	Placebo	Single dose	Outpatient	$P_{ET}CO_2$, SaO_2
Hui, 2014[39]	Parallel	20 (45)	Cancer (20)	55 (range 27-75)	Fentanyl[c]	30-350 µg[d]	Parenteral	Placebo	Single dose	Outpatient	SaO_2, RR
Jankelson, 1997[31]	Crossover	16 (69)	COPD (16)	69 (range 61-85)	Morphine	20 or 40 mg	Nebulized	Placebo	Single dose	Inpatient	SaO_2
Jensen, 2012[32]	Crossover	16 (58)	COPD (16)	70.5±2.3	Fentanyl	50 µg	Nebulized	Placebo	Single dose	Unclear	$P_{ET}CO_2$, SaO_2, RR, RD
Johnson, 2002[65]	Crossover	10 (100)	CHF (10)	67 (range 45-85)	Morphine	10-20 mg·day^{-1}	Oral	Placebo	4 days	Inpatient	$PaCO_2$, PaO_2, SaO_2, RR
Krajnik, 2009[48]	Parallel	10 (40)	Cancer (10)	55.5 (range 39-73)	Morphine	5 mg	Nebulized	2 types of nebulization	Single dose	Inpatient	$PaCO_2$, PaO_2, SaO_2
Light, 1989[33]	Crossover	13 (100)	COPD (13)	65.9 (range 58-70)	Morphine	0.8 mg·kg^{-1}	Oral	Placebo	Single dose	Unclear	$PaCO_2$, PaO_2, SaO_2, RR
Light, 1996[34]	Crossover	7 (100)	COPD (7)	66.4±3.3	Morphine	30 mg	Oral	Placebo	Single dose	Unclear	$P_{ET}CO_2$
Masood, 1995[53]	Crossover	12 (100)	COPD (12)	66.3±7.0	Morphine	Nebulised: 10 and 25 mg Parenteral: 1 and 2.5 mg	Nebulized and parenteral	Placebo	Single dose	Inpatient	SaO_2, RR
Mazzocato, 1999[40]	Crossover	9 (66)	Cancer (9)	73 (range 66-83)	Morphine	5 mg (or 150% of pretreatment dose)	Parenteral	Placebo	Single dose	Inpatient	SaO_2, RR, RD
Munck, 1990 (part 2)[43]	Crossover	21	COPD (21)	Median 67 (range 50-78)	Codeine	60 mg·day^{-1}	Oral	1 gram paracetamol	7 days	Inpatient	$PaCO_2$, PaO_2, SaO_2, RR

Table 1. Continued

First author, year	Design	Subjects n (% male)	Population (n)	Age years	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
Natalini, 2011[51]	Crossover	13 (43)	Trauma (3) COPD (3) Pneumonia (3) Stroke (2) Epilepsy (1) Peritonitis (1)	Median 78 (IQR 73-82)	Remifentanyl	0.05 μg·kg^{-1}·min^{-1}	Parenteral	Placebo	Single dose	Inpatient	$PaCO_2$, PaO_2, RR
Navigante, 2010[44]	Parallel	63	Cancer (31)	Median 55 (range 30-80)	Morphine[a]	22.5 (4.12) mg	Oral	Midazolam	5 days	Outpatient	SaO_2
Noseda, 1997[35]	Crossover	17 (76)	COPD (12) IPF (1) Cancer (3) CHF (1)	69 ±11	Morphine	10 or 20 mg	Nebulized	Placebo	Single dose	Inpatient	SaO_2, RR
Otulana, 2004 (phase 3)[49]	Crossover	19	Asthma (19)	Range 19-64	Morphine	2.2, 4.4 or 8.8 mg	Nebulized	3 doses	Single dose	Unclear	RR
Oxberry, 2011[41]	Crossover	35 (86)	CHF (35)	70.2±11.1	Morphine Oxycodone	20 mg·day^{-1} 10 mg·day^{-1}	Oral	Placebo	4 days	Outpatient	SaO_2, RR
Poole, 1998[42]	Crossover	16 (69)	COPD (16)	70.7±6.4	Morphine SR	Target: 40 mg (mean 25 mg)	Oral	Placebo	6 weeks	Outpatient	SaO_2
Rice, 1987[45]	Crossover	11 (100)	COPD (11)	Range 59-79	Codeine	120 mg	Oral	Promethazine	1 month	Unclear	$PaCO_2$, PaO_2
Robin[e], 1986[55]	Crossover	1 (0)	OLD	63	Hydromorphone	12 mg·day^{-1}	Rectal	Placebo	24 hours	Outpatient	$PaCO_2$, PaO_2
Schonhofer, 1998[50]	Crossover	20 (55)	Lung emphysema (20)	68.5±6.8	Morphine SR	Target: 90 mg (mean 49 mg)	Oral	Usual care	10 days	Inpatient	$PaCO_2$, PaO_2, RD
Shohrati, 2012[36]	Parallel	40 (100)	COPD (40)	No data	Morphine	1 mg·day^{-1}	Nebulized	Placebo	5 days	Inpatient	RR
Smith, 2009[56]	Crossover	2 (0)	Cancer (1) Unclear (1)	49 and 59	Fentanyl	25 μg	Nebulized	Placebo	Single dose	Inpatient	SaO_2, RR
Williams, 2003[66]	Crossover	16 (94)	CHF (16)	61±8.8	Diamorphine	1 or 2 mg	Parenteral	Placebo	Single dose	Unclear	$P_{ET}CO_2$, RR

Table 1. Continued

First author, year	Design	Subjects n (% male)	Population (n)	Age years	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
Woodcock, 1982[37]	Crossover	16	COPD (16)	No data	Dihydrocodeine	90 or 180 mg·day^{-1}	Oral	Placebo	2 weeks	Outpatient	$PaCO_2$, PaO_2
Allcroft, 2013[67]	Nonrandomized	13 (62)	COPD (13)	Median 78 (range 68-89)	Morphine	10 mg·day^{-1}	Oral		4 days	Inpatient/ outpatient	$PETCO_2$, SaO_2, RR, RD
Boyd, 1997[68]	Nonrandomized	15 (47)	Cancer (15)	73 (range 62-85)	Morphine	20 mg·day^{-1} or 130% of pretreatment dose	Oral		7-10 days	Inpatient/ outpatient	RR
Bruera, 1990[69]	Nonrandomized	20 (55)	Cancer (20)	64±17	Morphine	5 mg or 2.5 times pretreatment dose	Parenteral		Single dose	Inpatient	$PETCO_2$, SaO_2, RR
Bruera, 1993 (part 2)[26]	Nonrandomized	45	Cancer (45)	No data	Morphine[c]	Same dose as for pain treatment	Parenteral		Total of 312 doses	Unclear	RD
Clemens, 2007[70]	Nonrandomized	25 (44)	Cancer (25)	65.5±15.1	Morphine[f] Hydromorphone[f]	8.2 (7.5) mg MED 19.5 (1.8) mg MED	No data		Single dose	Inpatient	SaO_2, RR, RD
Clemens, 2008.1[59]	Nonrandomized	6 (67)	ALS (6)	57.0±6.9	Morphine[a]	6.3 (7.0) mg	Oral		Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Clemens, 2008.2[58]	Nonrandomized	14 (57)	Cancer (14)	Median 67 (range 40-84)	Hydromorphone[a]	2.5 (1.8) mg	Oral		Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Clemens, 2008.3[61]	Nonrandomized	27 (48)	Cancer (25) ALS (2)	Range 40-90	Morphine[a,f] Hydromorphone[a,f]	2.5-20.0 mg 0.5-6.0 mg	Oral		Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Clemens, 2009[62]	Nonrandomized	46 (54)	Cancer (46)	Range 40-90	Morphine[a,f] Hydromorphone[a,f]	2.5-20 mg 1-6 mg	Oral		Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Clemens, 2011[60]	Nonrandomized	26 (54)	Cancer (26)	66.0±13.6	Morphine[a] Hydromorphone[a]	8.4 (7.2) mg 4 (4.7) mg	Oral		Single dose	Inpatient	$PaCO_2$, SaO_2, RR, RD
Cohen, 1991[57]	Nonrandomized	8	Cancer (8)	61.9 (range 50-79)	Morphine[a]	120 mg·day^{-1}	Parenteral		60 hours	Unclear	$PaCO_2$, PaO_2, RR

Table 1. Continued

First author, year	Design	Subjects n (% male)	Population (n)	Age years	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
Coyne, 2002[71]	Nonrandomized	35 (43)	Cancer (33) Pulmonary embolism (1) AIDS (1)	56	Fentanyl	25 µg	Nebulized		Single dose	Inpatient	SaO_2, RR
Currow, 2011[72]	Nonrandomized	83 (64)	COPD (45) Cancer (24) ILD (10) Other (4)	74.6±9.1	Morphine	Target: 10-30 mg Phase II: 16.5 (8) mg Phase IV: 14.0 (6.3) mg	Oral		Target 3 months (mean 142 days)	Outpatient	RD
Gauna, 2008[73]	Nonrandomized	4 (50)	COPD and PF (2) Cancer (2)	Range 52-85	Fentanyl[c]	200-400 µg	Oral		Single dose	Inpatient	SaO_2, RR
Munck, 1990 (part 1)[43]	Nonrandomized	21	COPD (21)	Median 67 (range 50-78)	Codeine	60 and 120 mg	Oral		Single dose	Outpatient	$PaCO_2$, PaO_2, SaO_2, RR, RD
Otulana, 2004 (phase 4)[49]	Nonrandomized	6	Asthma (6)	No data	Morphine	17.6 mg	Nebulized		Single dose	Unclear	RR
Tanaka, 1999[74]	Nonrandomized	15 (53)	Cancer (15)	Median 61 (range 42-76)	Morphine	20 mg	Nebulized		Single dose	Inpatient	SaO_2, RR, RD

Notes: Data are presented as mean±SD, unless otherwise stated. [a] application of opioid for breakthrough breathlessness possible; [b] application of placebo for breakthrough breathlessness possible; [c] intervention prescribed for breakthrough breathlessness; [d] based on dose of current opioids for breakthrough breathlessness; [e] single-patient randomised controlled trial, which was terminated after the run-in phase and the placebo arm; data are therefore based on the run-in arm; [f] choice of dose or type of opioid depended on the general condition of the patient. **Abbreviations:** ALS, amyotrophic lateral sclerosis; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; MED, morphine equivalent dosing; MND, motor neurone disease; OLD, obstructive lung disease; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; $P_{ET}CO_2$, end-tidal carbon dioxide tension; PF, pulmonary fibrosis; RD, respiratory depressions; RLD, restrictive lung disease; RR, respiratory rate; SaO_2, arterial oxygen saturation; SR, sustained release.

Table 2. Summary of findings: Opioids compared to placebo for patients with chronic breathlessness due to advanced disease in inpatient and outpatient setting

	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	Participants (studies)	Quality of the evidence (GRADE)[b]
	Risk with placebo	Risk with opioids			
Mean $PaCO_2$	4.4 to 5.9 kPa	0.27 kPa higher (0.08 to 0.45 kPa higher) in the intervention group	-	146 (5 RCTs)	⊕◯◯◯ Very low[c,d,e]
Mean $P_{ET}CO_2$					
PTS	4.13 to 5.79 kPa	0.10 kPa higher (0.13 kPa lower to 0.34 kPa higher) in the intervention group	-	156 (4 RCTs)	⊕◯◯◯ Very low[c,d,e]
CFB	−0.05 kPa	0.14 kPa higher (0.05 kPa lower to 0.33 kPa higher) in the intervention group	-	14 (1 RCT)	⊕⊕◯◯ Low[d,e]
Mean PaO_2	9.0 to 10.4 kPa	0.26 kPa lower (0.68 kPa lower to 0.15 kPa higher) in the intervention group	-	118 (4 RCTs)	⊕◯◯◯ Very low[c,d,e]
Mean SaO_2					
PTS	84 to 100 %	0.47 % lower (0.87 to 0.07% lower) in the intervention group	-	312 (10 RCTs)	⊕◯◯◯ Very low[c,d,f]
CFB	−0.3 to 2.1 %	0.29 % lower (0.85% lower to 0.26% higher) in the intervention group	-	196 (4 RCTs)	⊕⊕◯◯ Low[c,d]
Mean RR					
PTS	18.6 to 40.0	0.86 lower (1.71 to 0.02 lower) in the intervention group	-	328 (9 RCTs)	⊕◯◯◯ Very low[c,d,f]
CFB	−4.2 to 0.0	0.80 lower (1.83 lower to 0.24 higher) in the intervention group	-	208 (4 RCTs)	⊕◯◯◯ Very low[d,e,f]

Notes: Data are presented as n, unless otherwise stated. [a] the risk (95% CI) in the intervention group is based on the assumed risk (95% CI) in the comparison group and the relative effect of the intervention; [b] GRADE working group grades of evidence were as follows. High quality: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the 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; [c] there were limitations in design and implementation, which suggest a risk of bias; [d] the majority of studies were not powered to detect changes in this outcome; [e] a small number of studies included; [f] patients who were pretreated with opioids were included. **Abbreviations:** CFB, change from baseline; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; $P_{ET}CO_2$, end-tidal carbon dioxide tension; PTS, post-treatment scores; RCT, randomised controlled trial; RR, respiratory rate; SaO_2, arterial oxygen saturation.

Effect on $P_{ET}CO_2$

The effect of opioid treatment on $P_{ET}CO_2$ was assessed in seven RCTs,[27,29,30,32,34,54,66] five of which could be included in the meta-analysis.[27,29,32,34,66] The meta-analysis showed a nonsignificant increase of the $P_{ET}CO_2$ (MD 0.13, 95% CI −0.02 to 0.27; I^2 0%; Figure 2b). The RCT by Light et al.[34] had a low variance compared to the other studies and consequently a high weight in the analysis. Therefore, as a sensitivity analysis, the meta-analysis was repeated, but with weighing based on the sample size. The effect on $P_{ET}CO_2$ was still not significant (MD 0.13, 95% CI −0.11 to 0.37; I^2 0%). The meta-regression revealed no influence from the context of assessment (p=0.375), the number of doses (p=0.679) or the route of administration (p=0.473) on the $P_{ET}CO_2$.

The effect on $P_{ET}CO_2$ was assessed in two NRTs.[67,69] These studies reported no significant change in $P_{ET}CO_2$.[67,69]

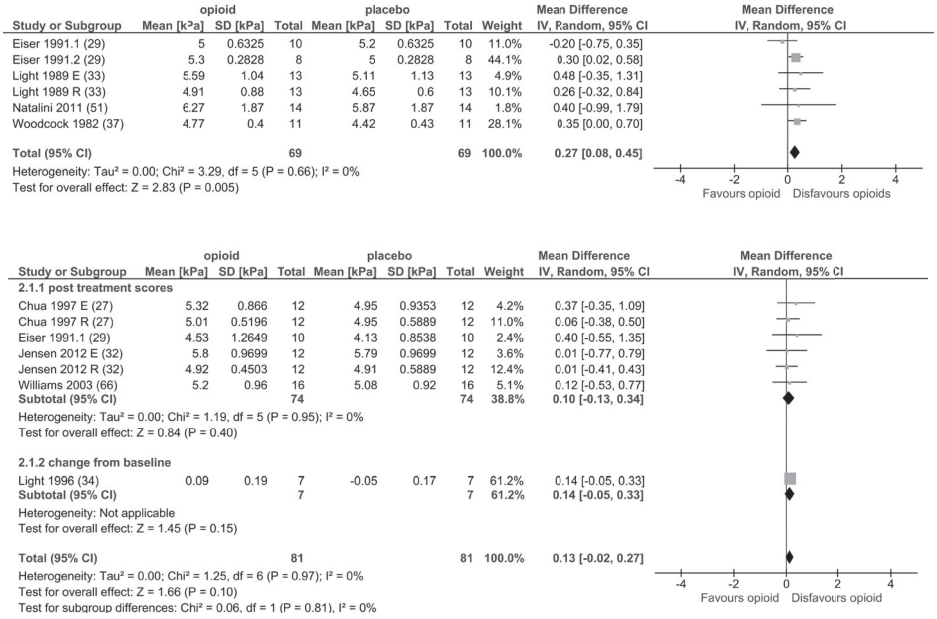

Figure 2. Effect of opioid treatment in patients with advanced disease on a) arterial carbon dioxide tension ($PaCO_2$); b) end-tidal carbon dioxide tension ($P_{ET}CO_2$).
Notes: Data are presented as mean±SD or mean difference (95% CI), unless otherwise stated. **Abbreviations:** E, measured on exertion; R, measured at rest.

Effect on PaO_2

The effect of opioid treatment on PaO_2 was assessed in nine RCTs,[29,33,37,43,45,50,51,55] four of which could be included in the meta-analysis.[29,33,37] The meta-analysis showed a nonsignificant decrease of the PaO_2 (MD −0.26, 95% CI −0.68 to 0.15; I^2 0%; Figure 3). The meta-regression revealed no influence from the context of assessment

(p=0.420; however, only one RCT was conducted during exercise) or the number of doses (p=0.815) on the PaO_2. Route of administration was not taken into account, since all RCTs administered the opioid systemically. One RCT examined the effect of opioids on PaO_2 during exercise.[33] The difference between the intervention and control groups after administration of morphine was statistically significant at maximal exercise (8.8 and 9.6 kPa, respectively; p<0.05).
The effect on PaO_2 was assessed in two NRTs.[43,57] One NRT found a significant decrease in PaO_2.[57] Finally, the effect on PaO_2 was assessed in one case report describing two cases.[64] In this study the opioids were nebulised for up to 15 days. PaO_2 was measured at rest. This study showed no significant effect of opioid treatment on PaO_2.

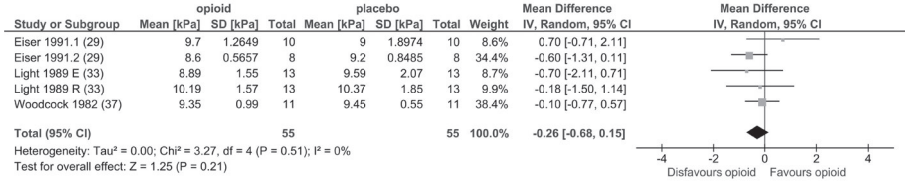

Figure 3. Effect of opioid treatment in patients with advanced disease on arterial oxygen tension (PaO_2).
Abbreviations: E, measured on exertion; R, measured at rest.

Effect on SaO_2

The effect of opioid treatment on SaO_2 was assessed in 24 RCTs,[25-33,35,38-44,47-49,52-54,56] 14 of which could be included in the meta-analysis.[26-33,35,38-42] The meta-analysis showed that SaO_2 decreased after opioid use (MD −0.41, 95% CI −0.73 to −0.08; I^2 0%; Figure 4). The study by Chua et al.[27] was the only RCT showing a significant difference in SaO_2 between the intervention and control groups at rest (99.3% and 100%, respectively; p=0.03). This RCT reported a variance of zero in the control group in rest and consequently had a high weight in the analysis. Therefore, as a sensitivity analysis the meta-analysis was repeated, but with weighing based on the sample size. The effect on SaO_2 was no longer significant (MD −0.31, 95% CI −1.06 to 0.45; I^2 0%). The meta-regression revealed no influence from the context of assessment (p=0.730), the number of doses (p=0.165) or the route of administration (p=0.538) on the SaO_2.

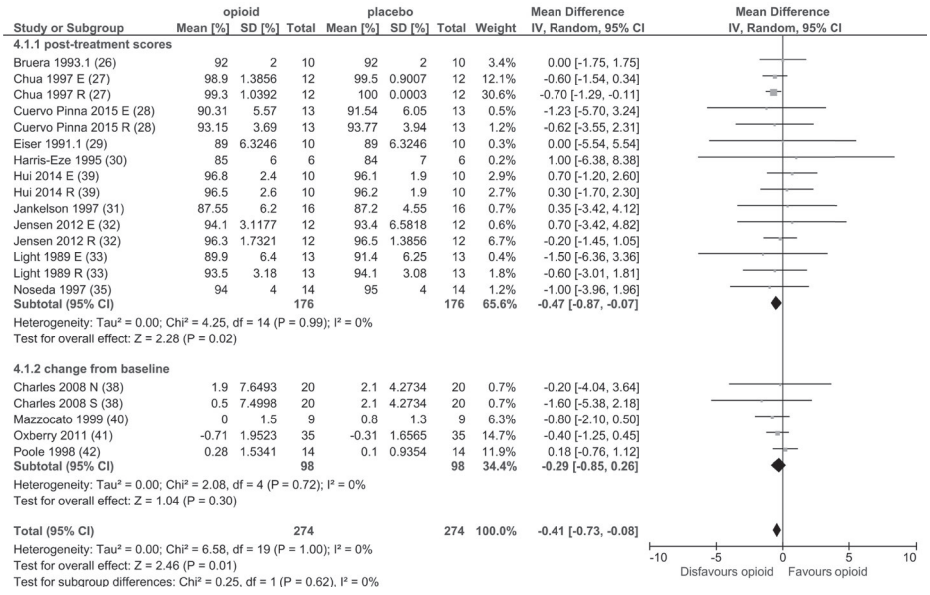

Figure 4. Effect of opioid treatment in patients with advanced disease on arterial oxygen saturation (SaO_2).
Abbreviations: E, measured on exertion; R, measured at rest.

Furthermore, the effect of opioids on SaO_2 was assessed in 12 NRTs.[43,58-62,67,69-71,73,74] One NRT showed a significant decrease in SaO_2 from 93% to 92% after a single dose of 120 mg codeine.[43] However, this decrease was temporary and not clinically relevant. Finally, the effect of opioids on SaO_2 was assessed in two POSs,[75,76] two ROSs[63,77] and three case reports describing seven cases.[64,78,79] In these studies, the opioids were administered systemically (n=3), nebulised (n=2) or via an unknown route (n=1). The opioids were prescribed as single dose or as repeated doses up to 3 months. In all studies, SaO_2 was measured at rest. None of these studies showed a significant effect of opioid treatment on SaO_2. In two RCTs[25,54] and one NRT[67] SaO_2 was measured, but no outcome data were reported.

Effect on respiratory rate

The effect of opioid treatment on respiratory rate was assessed in 23 RCTs,[25-28,30,32,33,35,36,38-41,43,46,47,49,51-53,56,65,66] 13 of which could be included in the meta-analysis.[25,26,30,32,33,35,36,38-41,65,66] The meta-analysis showed that treatment with opioids significantly decreased the respiratory rate (MD −1.10, 95% CI −1.49 to −0.71; I^2 0%; Figure 5). The study by Shohrati et al.[36] was the only RCT showing a significant difference in change in respiratory rate between the intervention and control groups (−1.5 and −0.1, respectively; p<0.001). This RCT had a low variance compared to the other studies and consequently a high weight in the analysis. Therefore, as

a sensitivity analysis, the meta-analysis was repeated, but with weighing based on the sample size. The effect on respiratory rate was no longer significant (MD −0.58, 95% CI −1.72 to 0.56; I^2 0%). The heterogeneity among the RCTs describing post-treatment scores was 0%. The meta-regression revealed no influence from the context of assessment (p=0.496), the number of doses (p=0.904) or the route of administration (p=0.139) on the respiratory rate.

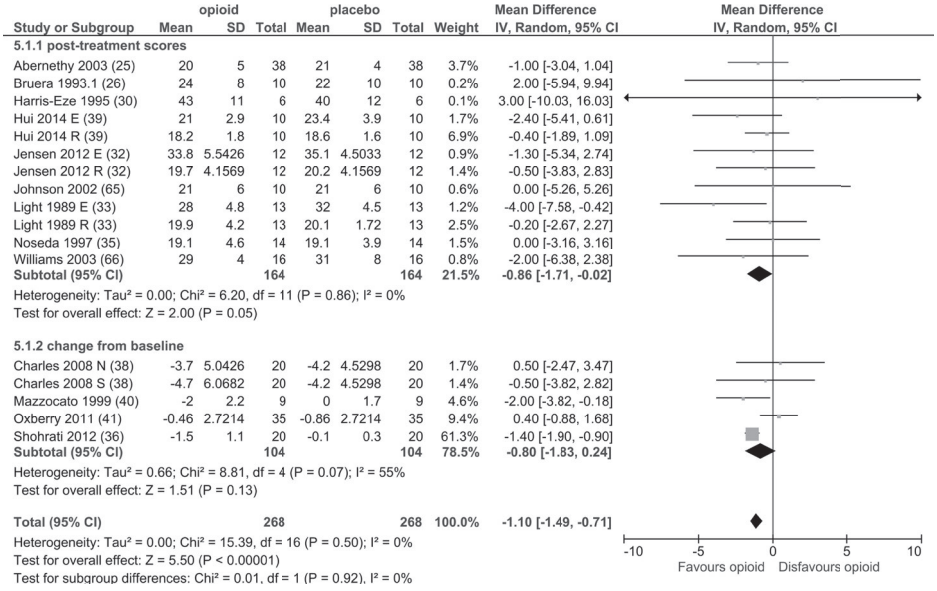

Figure 5. Effect of opioid treatment in patients with advanced disease on respiratory rate.
Abbreviations: E, measured on exertion; R, measured at rest; N: nebulised administration; S: systemic administration.

The effect on respiratory rate was also assessed in 15 NRTs.[43,49,57-62,67-71,73,74] These studies also showed that opioids caused no significant change in respiratory rate. Finally, the effect on respiratory rate was assessed in three POSs,[75,76,80] two ROSs[63,77] and four case reports describing ten cases.[64,78,79,81] In these studies, the opioids were administered systemically (n=4), nebulised (n=4) or via an unknown route (n=1). The opioids were prescribed as single dose or as repeated doses up to 3 months. In all studies, RR was measured at rest. These studies also showed that opioids caused no significant change in respiratory rate. In two RCTs[28,43] and one NRT,[43] respiratory rate was measured, but no outcome data were reported.

Occurrence of respiratory depression

The occurrence of respiratory depressions was reported in five RCTs,[25,32,40,47,50] 11 NRTs,[26,43,58-62,67,70,72,74] two POSs,[14,75] three ROSs[15,82,83] and four case reports describing ten cases.[13,64,79,84] Out of these 25 studies, 11 defined respiratory depression.[13,14,40,58-62,74,75,84] Definitions were based on an increase in $PaCO_2$ of >0.5 kPa or to >6.0 kPa, a decrease in respiratory rate of >10% or to <10 breaths·min^{-1} and a decrease in SaO_2 of >5% or to <90%. Hu et al.[14] observed a case of respiratory depression (defined as decrease in respiratory rate to <10 breaths·min^{-1}) in one patient with terminal cancer both at the beginning of the POS and two days prior to death. Kawabata and Kaneishi[15] reported three patients experiencing respiratory depressions (no definition given), which were not serious. It was not stated whether these patients were treated for pain or breathlessness. Lang and Jedeikin[13] described a case of respiratory depression (defined as respiratory rate of 4 to 5 breaths·min^{-1}, very poor respiratory effort and minimal wheezing over both lung fields) after administration of 4 mg nebulised morphine and 4 mg dexamethasone for breakthrough breathlessness in a patient already using 10 mg oral slow-release morphine three times per day and 10 mg oral immediate-release morphine when required for cancer-related pain.

Quality of the evidence

The quality of the evidence was assessed as very low to moderate for the different outcomes (Table 2). Only RCTs were included in this assessment. For all outcomes, the majority of the RCTs were small with insufficient power to assess respiratory adverse events and the quality was therefore downgraded. Furthermore, limitations in the design and implementation were observed. In several RCTs, patients who were pretreated with opioids were included, which had a negative effect on the quality of the evidence. Finally, only a small number of RCTs included assessment of $PaCO_2$ and PaO_2.

Discussion

Main findings

This systematic review on the occurrence of respiratory adverse effects following opioid treatment for breathlessness shows a great heterogeneity of treatment regimens and patient populations. Given this heterogeneity, we found no evidence that clinically relevant respiratory adverse effects are to be expected in patients with breathlessness who are treated with opioids, while included studies confirmed previous reports of opioid-related benefit for breathlessness. This suggests that clinicians' fears of respiratory obtundation with the use of low-dose opioids seem to be unfounded.

The meta-analysis showed an increase in $PaCO_2$ of 0.27 (0.09 to 0.46) kPa. Although this increase is statistically significant, it is not considered to be clinically relevant.[85] Indeed, the pooled mean±SD $PaCO_2$ was 5.35±1.08 kPa, so the mean difference in $PaCO_2$ was only 25% of the standard deviation. However, few RCTs reported on $PaCO_2$, and the quality of this evidence is assessed as very low. One NRT reported a significant deterioration of blood gases, but the participants received 120 mg parenteral morphine per day.[57] Given that 20 to 40% of oral morphine is bioavailable, this represents a much higher dose than the oral morphine doses required in the dose titration study (10 to 30 mg oral morphine per day)[72] or the oral morphine repeat dose trials (20 mg oral morphine per day).[25,41,65] The meta-analyses showed a significant decrease in SaO_2 of 0.41% (0.73 to 0.08%) and respiratory rate of 1.10 (1.49 to 0.71) breaths·min^{-1}. However, in both analyses one study had a high weighting due to a small variance. The statistical significance disappeared when the analyses were repeated weighted on sample size. In four cases, a diagnosis of respiratory depression was made during the study, but the definition was poorly stated. In three occasions the indication and dose were not clear.[15] In the fourth case, respiratory depression occurred in a patient with advanced metastatic cancer pretreated with opioids. The additive effect of both treatments, leading to a high dose of morphine, may have led to respiratory depression.[13] It is notable that no cases of respiratory depression were noted in the context of RCTs, with their close monitoring. Neither the meta-analyses of $P_{ET}CO_2$, PaO_2, SaO_2 and respiratory rate nor the studies that were not included in the meta-analyses showed a significant deterioration of these outcomes. The meta-regression did not provide a significant effect for the context of assessment (at rest or on exertion), the number of doses (single dose or multiple doses) or the route of administration (nebulised or systemic), which is surprising especially for the route of administration. Previous reviews have reported a different effect of opioids on breathlessness when administered systemically or nebulised.[5,6] The results of this meta-regression might be related to small effects within the included studies and the fact that only six studies included in the meta-analysis used nebulised opioid.

Six ongoing studies were identified. Three of those only examine a single or double dose of opioids and therefore will not illuminate the long-term effect. Of the three other studies, two have respiratory adverse effects as a secondary outcome, and the sample size calculation will therefore probably not be based on this outcome. Only the MORDYC (Morphine for Dyspnea in COPD) study focuses primarily on respiratory adverse effects, and the sample size calculation is based on the $PaCO_2$.[85] This study will add valuable information about the occurrence of respiratory adverse effects. Our findings are consistent with other reviews on opioids for chronic breathlessness[5,6,86] and episodic breathlessness.[87] These reviews included RCTs,[5,6,86,87] NRTs[6,86] and case reports.[87] The authors of these reviews found no clinically relevant effect on blood gases, oxygen saturation or respiratory depression after treatment with different types of opioids in patients with advanced disease.

In hypoxic patients with cancer, an improvement of SaO_2 was reported.[6] However, these reviews only included 39 studies, and meta-analyses could not be performed due to limited results on respiratory adverse effects. Furthermore, the focus of these reviews was on the effect of opioid treatment on breathlessness, and search terms for respiratory adverse effects were not included.

Limitations of the included studies

First, the risk of bias of the included studies was often difficult to estimate. The outcomes of interest in the current review were secondary outcomes in the majority of the included studies, and therefore the method of outcome assessment was often not described. The method of randomisation or allocation concealment was inadequately described in most studies. Since it was difficult to score the risk of bias and to set a cut-off point, we did not include a sensitivity analysis including only the studies with a low risk of bias. *Second*, there was great heterogeneity in the dosing regimens and comparators used. The prescribed doses ranged between the studies, with eight studies prescribing high doses of opioids. In 34 experimental studies, one observational study and seven cases, only a single dose of opioids was prescribed, so the long-term effect was not assessed. Seven RCTs did not include a placebo group, but used different doses, other medication or usual care as comparator. *Third*, the patient populations were heterogeneous. In some studies patients had to be opioid-naïve, but not in others; patients could continue opioids for pain or the dose of the study medication was based on current analgesic treatment. *Fourth*, the included studies had a small sample size. The experimental studies included between one and 83 participants, with only six studies including a sample size of ≥30 participants per treatment group. These studies included outcomes of respiratory adverse effects, but were underpowered to properly assess a change in these outcomes. The observational studies used larger sample sizes, but only a proportion of these patients received opioids for breathlessness. In some studies, the results accounted for the entire group, making it impossible to draw conclusions for the subgroup of our interest. *Fifth*, the definition of respiratory depression differed between studies. The most reliable assessment of respiratory depression is based on the PaO_2 and $PaCO_2$. Measurement of SaO_2 is less reliable.[88] Some authors included respiratory rate as a measure of respiratory depression, because this is easier to estimate. Only 11 studies defined respiratory depression, and eight used a decrease in SaO_2 as part of the definition. Only four also included an increase of $PaCO_2$. *Finally*, five studies mentioned the assessment of respiratory outcomes in their method section, but didn't include the results (n=3) or only reported the baseline data (n=2). Furthermore, 25 studies reported on the occurrence of respiratory depression, but only nine of them mentioned the assessment of respiratory depression in their methods section. Therefore, it is not known if a respiratory depression occurred in any of the remaining 42 studies.

Strengths and limitations of the current review

Our study has several strengths. We included several study types; although RCTs yield the most reliable evidence, observational studies and case reports are closer to daily clinical practice. Furthermore, we included studies that were published in five languages. Because of the large number of included studies, we were able to present the current knowledge of six different outcomes of respiratory adverse effects, and we were able to perform meta-analyses on five of these. This provides an overall estimate of the effect of opioid treatment on these outcomes.

Our review has several limitations. *First*, we only searched four databases. Due to publication bias, we might have failed to identify negative results. However, we also searched one trial register, sought expert opinions and hand-searched the reference lists of important reviews in the field of opioid treatment for chronic breathlessness. We identified a large number of studies, decreasing the chance that we missed important studies. *Second*, several RCTs could not be included in the meta-analyses because of reasons discussed earlier. *Third*, we combined results from studies with different contexts of assessment, different number of doses and different route of administration; however, this was done only after the meta-regression which did not yield evidence that these moderators had an effect on the outcome. The number of studies used for this analysis was in some cases very low, making the power to detect effects questionable. However, due to the robustness of the results (i.e. no single moderator was significant in any of the analyses), we combined all measures to be pooled. *Fourth*, the patient populations were too diverse to specify the results for different populations. We primarily expect that patients with COPD and chronic respiratory failure are more at risk of respiratory adverse effects than patients with cancer or heart failure, for example. Most of the studies included patients with a specified primary diagnosis (n=54), of which 16 studies only included patients with COPD. However, from these populations it is not known which patients experienced chronic respiratory failure. *Fifth*, we used the Cochrane risk of bias tool to assess the risk of bias in RCTs and NRTs. This tool is designed for use in RCTs, but there was no appropriate alternative to use in NRTs. After assessment of the risk of bias was completed, the Risk of Bias in Nonrandomized Studies - of Interventions (ROBINS-I) tool was published.[89] This might have been a better tool to assess the risk of bias in NRTs and can be used in future studies. *Finally*, we included both crossover trials and parallel trials in the meta-analysis together, and we analysed the crossover trials as if they were parallel trials. This might result in a unit of analysis error, leading to an underweighting of the crossover trials. Since only two studies included in the meta-analyses of SaO_2 and respiratory rate were parallel trials and the remaining studies were crossover trials, we assume this influence to be negligible.

Implications for clinical practice and future research

Patients are willing to consider opioid treatment for chronic breathlessness, despite the occurrence of adverse effects, and report improvement of quality

of life and relief of breathlessness as their main reasons.[12] However, physicians remain reluctant to prescribe opioids for chronic breathlessness, because of fear of adverse clinical outcomes, among others.[9-12] A recent large observational study of older adults with COPD by Vozoris et al.[90] showed an association between new prescription of opioid and a small, but statistically significant increase in 30-day mortality and emergency visits. However, palliative care patients (and thus those who form the main group for whom opioids would be prescribed for breathlessness) were excluded and other differences between patients with and without opioid use might explain these findings. In contrast, a registry study of people with advanced COPD on long-term oxygen therapy, with four years of follow-up found no association with either hospital admission or survival in people taking ≤30 mg of oral morphine per day.[91]

This review has shown that the current evidence on respiratory adverse effects of opioid treatment in chronic breathlessness is inconsistent and heterogenic. Only one serious episode of respiratory depression is described and that in the context of high-dose opioids. Based on the evidence included in this review, low-dose opioids can be considered as safe treatment for chronic breathlessness in the context of good clinical care and appropriate monitoring. However, the studies that have been conducted are mostly of low quality, short duration and not designed to assess the effect of low-dose opioids on respiratory adverse effects. A long-term, well-powered randomised controlled trial, such as the MORDYC study, is needed. Moreover, including a common respiratory outcome set in all trials of opioids for breathlessness, so that a more robust synthesis could be conducted, is recommended.

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Supplementary Material

Supplemental Methods – Search strategies

A. Search strategy in Pubmed

Breathlessness	1	dyspnoea/drug therapy[Mesh Terms]
	2	dyspn*[Title/Abstract]
	3	breathless*[Title/Abstract]
	4	((breath*[Title/Abstract]) AND labour*[Title/Abstract])
	5	((short*[Title/Abstract]) AND breath*[Title/Abstract])
	6	breathing difficult*[Title/Abstract]
	7	1 OR 2 OR 3 OR 4 OR 5 OR 6
Opioid	8	analgesics, opioid/adverse effects[Mesh Terms]
	9	analgesics, opioid/therapeutic use[Mesh Terms]
	10	opioid*[Title/Abstract]
	11	opiate*[Title/Abstract]
	12	codeine/adverse effects[Mesh Terms]
	13	codeine/therapeutic use[Mesh Terms]
	14	codeine[Title/Abstract]
	15	heroin/adverse effects[Mesh Terms]
	16	heroin/therapeutic use[Mesh Terms]
	17	diamorphine[Title/Abstract]
	18	fentanyl/adverse effects[Mesh Terms]
	19	fentanyl/therapeutic use[Mesh Terms]
	20	fentanyl[Title/Abstract]
	21	dihydrocodeine[Supplementary Concept]
	22	dihydrocodeine[Title/Abstract]
	23	morphine/adverse effects[Mesh Terms]
	24	morphine/therapeutic use[Mesh Terms]
	25	morphine[Title/Abstract]
	26	oxycodone/adverse effects[Mesh Terms]
	27	oxycodone/therapeutic use[Mesh Terms]
	28	oxycodone[Title/Abstract]
	29	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28
	30	animals[Mesh Terms] NOT humans[Mesh Terms]
	31	(#7 AND #29) NOT #30
	32	Limit #31 to article types case reports, clinical studies, clinical trials, comparative studies, multicentre studies, observational studies, randomized controlled trials.

B. Search strategy in Embase

Breathlessness	1	exp dyspnea/dt [Drug Therapy]
	2	dyspn*.mp [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
	3	breathless*.mp
	4	“breath* labour*”.mp
	5	“short* of breath*”.mp
	6	“breath* difficult*”.mp
	7	1 OR 2 OR 3 OR 4 OR 5 OR 6

Opioids	8	exp opiate/ae, dt [Adverse Drug Reaction, Drug Therapy]
	9	opioid*.mp
	10	opiate*.mp
	11	exp codeine/ae, dt [Adverse Drug Reaction, Drug Therapy]
	12	codeine.mp
	13	exp diamorphine/ae, dt [Adverse Drug Reaction, Drug Therapy]
	14	diamorphine.mp
	15	exp fentanyl/ae, dt [Adverse Drug Reaction, Drug Therapy]
	16	fentanyl.mp
	17	exp dihydrocodeine/ae, dt [Adverse Drug Reaction, Drug Therapy]
	18	dihydrocodeine.mp
	19	exp morphine/ae, dt [Adverse Drug Reaction, Drug Therapy]
	20	morphine.mp
	21	exp oxycodone/ae, dt [Adverse Drug Reaction, Drug Therapy]
	22	oxycodone.mp
	23	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
	24	7 AND 23
	25	Limit 24 to human
	26	Limit 25 publication type to *Journal: Article*

C. Search strategy in CENTRAL

Breathlessness	#1	MeSH descriptor: [Dyspnea] explode all trees and with qualifier(s): [Drug therapy – DT]
	#2	dyspn*.ti,ab,kw (Word variations have been searched)
	#3	breathless*.ti,ab,kw (Word variations have been searched)
	#4	"breath* labour*".ti,ab,kw (Word variations have been searched)
	#5	"short* of breath*".ti,ab,kw (Word variations have been searched)
	#6	"breath* difficult*".ti,ab,kw (Word variations have been searched)
	#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
Opioids	#8	MeSH descriptor: [Analgesics, Opioid] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU]
	#9	opioid*.ti,ab,kw (Word variations have been searched)
	#10	opiate*.ti,ab,kw (Word variations have been searched)
	#11	MeSH descriptor: [Codeine] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU]
	#12	codeine.ti,ab,kw (Word variations have been searched)
	#13	MeSH descriptor: [Heroin] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU]
	#14	diamorphine.ti,ab,kw (Word variations have been searched)
	#15	MeSH descriptor: [Fentanyl] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU]
	#16	fentanyl.ti,ab,kw (Word variations have been searched)
	#17	dihydrocodeine.ti,ab,kw (Word variations have been searched)
	#18	MeSH descriptor: [Morphine] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU]
	#19	morphine.ti,ab,kw (Word variations have been searched)
	#20	MeSH descriptor: [Oxycodone] explode all trees and with qualifier(s): [Adverse effects – AE, Therapeutic use – TU]
	#21	oxycodone.ti,ab,kw (Word variations have been searched)
	#22	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
	#23	#7 AND #22
	#24	Limit #23 to *trials*

D. Search strategy in CINAHL

Breathlessness	S1	(MH "Dyspnea+/DT")
	S2	TI dyspn* OR AB dyspn*
	S3	TI breathless* OR AB breathless*
	S4	TI "breath* labour*" OR AB "breath* labour*"
	S5	TI "short* of breath*" OR AB "short* of breath*"
	S6	TI "breath* difficult*" OR AB "breath* difficult*"
	S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
Opioids	S8	(MH "Analgesics, Opioid+/AE/TU")
	S9	TI opioid* OR AB opioid*
	S10	TI opiate* OR AB opiate*
	S11	(MH "Codeine+/AE/TU ")
	S12	TI codeine OR AB codeine
	S13	(MH "Heroin+/AE/TU ")
	S14	TI diamorphine OR AB diamorphine
	S15	(MH "Fentanyl+/AE/TU ")
	S16	TI fentanyl OR AB fentanyl
	S17	TI dihydrocodeine OR AB dihydrocodeine
	S18	(MH "Morphine+/AE/TU ")
	S19	TI morphine OR AB morphine
	S20	(MH "Oxycodone+/AE/TU ")
	S21	TI oxycodone OR AB oxycodone
	S22	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
	S23	S7 AND S21; Limiters - Human

E. Search strategy in ClinicalTrials.gov

Breathlessness	S1	Dyspnea (condition/disease)
	S2	Dyspnea (other terms)
	S3	Dyspnoea (other terms)
	S4	Breathlessness (condition/disease)
	S5	Breathlessness (other terms)
	S6	Breath shortness (condition/disease)
	S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
Opioids	S8	Opioids (intervention/treatment)
	S9	Opioid analgesic (intervention/treatment)
	S10	Analgesics, opioid (intervention/treatment)
	S11	Opiate (intervention/treatment)
	S12	Opioid (other terms)
	S13	Analgesic (other terms)
	S14	Codeine (intervention/treatment)
	S15	Codeine (other terms)
	S16	Diamorphine (intervention/treatment)
	S17	Diamorphine (other terms)
	S18	Fentanyl (intervention/treatment)
	S19	Fentanyl (other terms)
	S20	Dihydrocodeine (intervention/treatment)
	S21	Dihydrocodeine (other terms)
	S22	Morphine (intervention/treatment)
	S23	Morphine (other terms)
	S24	Oxycodone (intervention/treatment)
	S25	Oxycodone (other terms)
	S26	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
	S27	S7 AND S26

Supplemental Tables

Table S1. Patient characteristics, study design and results of observational studies

First author, year	Design	Subjects n (% male)	Population (n)	Age years (n)	Opioid	Dose (mg·day^{-1})	Administration	Duration (n)	Patient setting	Outcomes: difference (n) *Definition of RD*
Allen, 2005[1]	Prospective	11 (27)	IPF (11)	68 (range 78-92)	Diamorphine	2.5-5.0	Parenteral	Single dose	Inpatient	SaO_2: 0% RR: -2 breaths·minute^{-1} RD: 0 *Change in vital signs or oxygen saturation*
Colman, 2015[2]	Retrospective	64 (45) 59 received opioids	Patients awaiting lung transplantation; ILD (51) BO (5) COPD (4) PH (4)	59.4±9.4	Morphine or hydromorphone[a]	Median dose: SR: 30 MED (range 20-840) IR: 15 MED (range 6-60) AN: no data	Oral	Median follow-up: 153 days	Inpatient/ outpatient	RD: 0
Farncombe, 1994[3]	Retrospective	54 (43)	Cancer (40) ORD (3) RRD (3) Cardiac disease (6) AIDS (1) Bowel obstruction (1)	62 (range 21-90)	Morphine[b] Hydromorphone[b] Codeine[b] Anileridine[b]	30-180 6-120 90-360 150-300	Nebulized	1-3 doses (12) 1-2 days (8) 3-14 days (17) > 15 days (17)	Inpatient/ outpatient	$PaCO_2$: no significant change (4) SaO_2: no significant change (4) RR: 10-30% decrease, but non below 16 breaths·minute^{-1} (8)
Hu, 2014[4]	Prospective	136 (57) 27 used opioid for breathlessness at admission and 36 2 days prior to death	Cancer (136)	≤ 18 (3) 19-35 (6) 36-50 (27) 51-64 (31) ≥ 65 (69)	Morphine	At admission: 37.7±38.6 MED Prior to death: 44.7±52.3 MED	Oral, parenteral, or combined	No data	Inpatient	RD: 1 (also at start of study) *Decrease in RR to less than 10 minute^{-1}.*

Table S1. Continued

First author, year	Design	Subjects n (% male)	Population (n)	Age years (n)	Opioid	Dose (mg·day^{-1})	Administration	Duration (n)	Patient setting	Outcomes: difference (n) ***Definition of RD***
Kanemoto, 2007[5]	Retrospective	337 (74) 92 reported breathlessness and received morphine	Cancer (212) IIP/CDPF (47) Pneumonia (41) COPD (22) Bronchiectasis (7) Tuberculosis (3) Pyothorax (2) PH (1) Thromboembolism (1) Pneumoconiosis (1)	72 (range 22-96)	Morphine	No data	Parenteral	No data	Inpatient	RD: 0
Kawabata, 2013[6]	Retrospective	95 (55) 44 administrations for episodes of breathlessness	Cancer (95)	71.7 (range 47-92)	Oxycodone[b]	44.6 (range 5.5-206.6)	Parenteral	Mean: 14.4 days	Inpatient	RD: 3
Oxberry, 2013[7]	Prospective	33 (85)	CHF (33)	71.9±9.1	Morphine or oxycodone vs. placebo	Morphine: 20 Oxycodone: 10	Oral	3 months	Outpatient	SaO_2: -1% in users, +1% in non-users RR: -1 breaths·minute^{-1} in users, -2 breaths·minute^{-1} in nonusers
Pang, 2016[8]	Prospective	16 (50)	Cancer (16)	63.6±13.5	Fentanyl	Responders: 0.22±0.17 Nonresponders: 0.28±0.20	Parenteral	24 hours	Inpatient	RR: -4 breaths·minute^{-1} in responders; -2 breaths·minute^{-1} in nonresponders[c]

Table S1. Continued

First author, year	Design	Subjects n (% male)	Population (n)	Age years (n)	Opioid	Dose (mg·day^{-1})	Administration	Duration (n)	Patient setting	Outcomes: difference (n) ***Definition of RD***
Sporer, 2006[9]	Retrospective	319 (47) 20 received morphine	ADHF (319)	77±12	Morphine	No data	No data	No data	Outpatient	SaO_2: no change (no data shown) RR: no change (no data shown)

Notes: [a] intervention is started on an as needed basis and transitioned to standing immediate-release opioids or sustained release opioids (with or without immediate-release opioids as needed) as tolerated; [b] application of opioid for breakthrough breathlessness possible [c] median change. **Abbreviations:** ADHF, acute decompensated heart failure; AIDS, acquired immune deficiency syndrome; AN, opioids on "as needed" basis; BO, bronchiolitis obliterans; CDPF, collagen disease-related pulmonary fibrosis; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IR, immediate-release opioids; MED, morphine equivalent dose; ORD, obstructive respiratory disease; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PH, pulmonary hypertension; RD, respiratory depressions; RR, respiratory rate; RRD, restrictive respiratory disease; SaO_2, arterial oxygen saturation; SR, sustained-release opioids.

Table S2. Patient characteristics and results of case reports

First author, year	Gender	Diagnosis	Age years	Opioid	Dose	Administration	Duration	Pre-treatment	Patient setting	Outcomes
Benitez-Rosario, 2005[10]	Female	Lung cancer	67	Fentanyl[a]	1200 µg	Oral	Single dose	400 mg intravenous morphine·day^{-1}	Inpatient	SaO_2: 90 to 91% RR: 22 to 14 breaths·minute^{-1}
	Male	Lung cancer	52	Fentanyl[a]	400 µg	Oral	2 doses in 30 min	90 mg SR morphine·day^{-1}	Inpatient	SaO_2: remained 93% RR: 20 to 18 breaths·minute^{-1}
	Female	Colon cancer	57	Fentanyl[a]	400 µg	Oral	Single dose	15 mg intravenous morphine·day^{-1}	Inpatient	SaO_2: remained 89% RR: remained 20 breaths·minute^{-1}
Farncombe, 1993[11]	Male	IPF	73	Morphine	30-150 mg	Nebulized	3 months	No	Inpatient	RR: slight decrease RD: no
	Male	IPF	68	Morphine	30-105 mg	Nebulized	At least 2 weeks	No	Inpatient	RD: no
	Male	CAD and COPD	74	Morphine	2.5 mg	Nebulized	Single dose	Intravenous morphine	Inpatient	$PaCO_2$: 7.2 to 6.4 kPa PaO_2: 8.5 to 9.9 kPa SaO_2: 87 to 93% RR: 32 to 28 breaths·minute^{-1} RD: no
	Female	CHF and COPD	72	Morphine	2.5 mg	Nebulized	Single dose	Intravenous morphine	Inpatient	$PaCO_2$: 4.8 to 4.7 kPa PaO_2: 12.4 to 12.7 kPa SaO_2: remained 98% RR: 30 to 26 breaths·minute^{-1} RD: no
Farncombe, 1994[12]	Male	Lung cancer, CHF and COPD	91	Morphine	60-90 mg·day^{-1}	Nebulized	At least 2 days	30 mg nebulized morphine·day^{-1}	Inpatient	RR: 36 to 26 breaths·minute^{-1}
	Female	Lung cancer	61	Hydromorphone[a]	48 mg·day^{-1}	Nebulized	No data	±480 mg oral hydromorphone·day^{-1}	Outpatient	RR: 34 to 26 breaths·minute^{-1}

Table S2. Continued

First author, year	Gender	Diagnosis	Age years	Opioid	Dose	Administration	Duration	Pre-treatment	Patient setting	Outcomes
Lang, 1997[13]	Female	Probably primary lung cancer with metastases	74	Morphine[a]	4 mg	Nebulized	Single dose	30 mg oral morphine·day^{-1}	Inpatient	RD: yes
Sitte, 2008[14]	Male	Lung cancer	73	Fentanyl[a]	150 µg	Nasal	Single dose	No data	Outpatient	SaO_2: 62 to 94% RR: 30 to 12 breaths·minute^{-1} RD: no
	Female	CHF, COPD and PH	88	Fentanyl[a]	1000 µg	Nasal	Single dose	No data	Outpatient	SaO_2: 65 to 75% RR: 40-50 to 20 breaths·minute^{-1} RD: no
	Male	ILD	72	Fentanyl[a]	400 µg· administration^{-1}	Nasal	Two weeks	No	Outpatient	RD: no
Sitte, 2009[15]	Male	COPD and lung cancer	85	Fentanyl[a]	2000-4000 µg·day^{-1}	Nasal	No data	32 mg SR hydromorphone·day^{-1}	Outpatient	RD: no
	Male	Lung cancer	53	Fentanyl	1200 µg·day^{-1} + 200 µg· episode^{-1}	Parenteral and nasal	No data	No data	Outpatient	RD: no

Notes: [a] intervention prescribed for an episode of breakthrough breathlessness. **Abbreviations:** CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PH, pulmonary hypertension; RD, respiratory depressions; RR, respiratory rate; SaO_2, arterial oxygen saturation; SR, sustained-release.

Table S3. Characteristics and study design of ongoing studies

Study name	Clinical-Trials number	Design	Estimate sample size	Population	Opioid	Dose	Administration	Comparison	Duration	Patient setting	Included outcomes
-	NCT02454751	NRT, NB, crossover	20	CHF	Fentanyl	50 µg	Nebulized	No treatment	Single dose	Outpatient	Secondary: SaO_2, RR pre- and post-exercise
-	NCT03018756	RCT, DB, crossover	20	IPF	Fentanyl	100 µg	Nebulized	Placebo	Single dose	Outpatient	Secondary: RR pre- and post-exercise
MORPHILD	NCT02622022	RCT, DB, parallel	36	ILD	Morphine	20-40 $mg{\cdot}day^{-1}$	Oral	Placebo	One week	Unknown	Secondary: SaO_2 in rest
MORDYC	NCT02429050	RCT, DB, parallel	124	COPD	Morphine SR	20-30 $mg{\cdot}day^{-1}$	Oral	Placebo	Four weeks	Outpatient	Primary: $PaCO_2$, PaO_2, SaO_2, RR in rest
DYS-NOC	NCT02801838	NRT, SB, parallel	50	ICU patients	Morphine	10 mg	No data	No treatment	Single or double dose	Inpatient	Secondary: blood gases in rest
BEAMS	NCT02720822	RCT, DB, parallel	171	COPD	Morphine SR	8, 16, 24 or 32 mg	Oral	Placebo	Three weeks	Outpatient	Secondary: $P_{ET}CO_2$, SaO_2 in rest

Table S4. Risk of bias of randomized controlled trials

First author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other sources of bias
Abernethy, 2003[16]	+	+	+	+	+	–	–
Allard, 1999[17]	?	+	+	+	+	+	+
Beauford, 1993[18]	?	?	+	?	+	–	–
Bruera, 1993 (part 1)[19]	?	?	?	?	+	+	–
Charles, 2008[20]	+	+	+	+	+	+	–
Chua, 1997[21]	?	?	+	?	+	+	–
Cuervo Pinna, 2015[22]	?	?	+	?	+	–	+
Eiser, 1991 (part 1)[23]	?	?	?	?	+	+	–
Eiser, 1991 (part 2)[23]	?	?	?	?	+	+	–
Gamborg, 2013[24]	?	?	+	?	+	–	+
Grimbert, 2004[25]	?	+	+	+	+	–	+
Harris-Eze, 1995[26]	?	+	+	+	+	+	+
Hui, 2014[27]	+	+	+	+	+	+	–
Jankelson, 1997[28]	?	+	+	+	+	+	–
Jensen, 2012[29]	?	+	+	+	–	+	+
Johnson, 2002[30]	+	+	+	+	+	+	+
Krajnik, 2009[31]	?	?	–	–	+	–	+
Light, 1989[32]	?	?	–	–	+	+	–
Light, 1996[33]	?	?	+	?	+	+	?
Masood, 1995[34]	?	?	+	?	+	–	+
Mazzocato, 1999[35]	?	?	+	?	+	+	+
Munck, 1990 (part 2)[36]	?	?	?	?	–	+	+
Natalini, 2011[37]	+	+	+	+	+	+	+
Navigante, 2010[38]	+	+	–	–	+	–	+
Noseda, 1997[39]	?	?	+	+	+	+	+
Otulana, 2004 (phase 3)[40]	–	–	–	–	?	–	–
Oxberry, 2011[41]	+	+	+	+	+	+	+
Poole, 1998[42]	+	+	?	+	+	+	+
Rice, 1987[43]	+	?	?	?	+	+	+
Robin, 1986[44]	+	+	–	–	–	+	+
Schonhofer, 1998[45]	–	–	–	–	–	+	–
Shohrati, 2012[46]	?	?	+	?	+	+	–
Smith, 2009[47]	?	?	+	+	–	+	?
Williams, 2003[48]	?	?	+	+	+	+	–
Woodcock, 1982[49]	?	?	+	+	–	?	–

Notes: + low risk of bias; **–** high risk of bias; **?** unclear risk of bias.

Table S5. Risk of bias of nonrandomized trials

First author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other sources of bias
Allcroft, 2013[50]	–	–	–	–	+	–	+
Boyd, 1997[51]	–	–	–	–	+	+	+
Bruera, 1990[52]	–	–	–	–	+	+	+
Bruera, 1993 (part 2)[19]	–	–	–	–	+	+	–
Clemens, 2007[53]	–	–	–	–	+	+	+
Clemens, 2008.1[54]	–	–	–	–	+	+	+
Clemens, 2008.2[55]	–	–	–	–	+	+	+
Clemens, 2008.3[56]	–	–	–	–	+	+	+
Clemens, 2009[57]	–	–	–	–	+	+	+
Clemens, 2011[58]	–	–	–	–	+	+	+
Cohen, 1991[59]	–	–	–	–	+	+	+
Coyne, 2002[60]	–	–	–	–	–	+	+
Currow, 2011[61]	–	–	–	–	+	+	+
Gauna, 2008[62]	–	–	–	–	+	+	–
Munck, 1990 (part 1)[36]	–	–	–	–	+	–	+
Otulana, 2004 (phase 4)[40]	–	–	–	–	?	–	–
Tanaka, 1999[63]	–	–	–	–	+	+	–

Notes: + low risk of bias; **–** high risk of bias; **?** unclear risk of bias.

Table S6. Risk of bias of prospective observational studies

First author, year	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest at start of study	Comparability of cohorts	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total
Allen, 2005[1]	★		★	★		★	★	★	6
Hu, 2004[4]	★		★					★	3
Oxberry, 2013[7]	★	★					★	★	4
Pang, 2016[8]	★		★	★			★	★	5

Table S7. Results of randomized controlled trials

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD number *Definition*
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Abernethy, 2003[16]	-	-	-	-	-	-	Excluded (no data shown)	-	At rest	I: 20 (5) C: 21 (4)	0
Allard, 1999[17]	-	-	-	-	-	-	-	-	At rest	O: -1.6 (2.3)[a,b]	-
Beauford, 1993[18]	-	-	At rest and on exertion (Emax)	No change (no data shown)	-	-	Excluded (baseline data shown)	-	-	-	-
Bruera, 1993 (part 1)[19]	-	-	-	-	-	-	At rest	I: 92 (2) C: 92 (2)	At rest	I: 24 (8) C: 22 (10)	-
Charles, 2008[20]	-	-	-	-	-	-	At rest	N: +1.9 (6.1)[b] S: +0.2 (6.0)[b] C: +2.1 (3.4)[a,b]	At rest	N: -3.7 (5.0)[a,b] S: -4.7 (6.1)[b] C: -4.2 (4.5)[a,b]	-
Chua, 1997[21]	-	-	At rest and on exertion (Bruce), %	R-I: 5.0 (0.5) R-C: 4.6 (0.6) E-I: 5.3 (0.9) E-C: 5.0 (0.9)	-	-	At rest and on exertion (Bruce)	R-I: 99.3 (1.0)[c] R-C: 100 (0)[c] E-I: 98.9 (1.4) E-C: 99.5 (0.9)	At rest and on exertion (Bruce)	R-I: 14 R-C: 18 E-I: 23 E-C: 26	-
Cuervo Pinna, 2015[22]	-	-	-	-	-	-	At rest and on exertion (6MWT)	R-I: 93.2 (3.7) R-C: 93.8 (3.9) E-I: 90.3 (5.6) E-C: 91.5 (6.1)	Excluded (no data shown)	-	-

Table S7. Continued

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD number *Definition*
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Eiser, 1991 (part 1)[23]	At rest, arterial	2.5 mg: 5.4 (0.9) 5 mg: 5.0 (0.6) C: 5.2 (0.6)	At rest	2.5 mg: 4.4 (0.9) 5 mg: 4.5 (1.3) C: 4.1 (0.9)	At rest, arterial	2.5 mg: 8.6 (1.3) 5 mg: 9.7 (1.3) C: 9.0 (1.9)	At rest	2.5 mg: 90 (6.3) 5 mg: 89 (6.3) C: 89 (6.3)	-	-	-
Eiser, 1991 (part 2)[23]	At rest, arterial	I: 5.3 (0.3)[d] C: 5.0 (0.3)	-	-	At rest, arterial	I: 8.6 (0.6)[d] C: 9.2 (0.8)	-	-	-	-	-
Gamborg, 2013[24]	-	-	-	-	-	-	At rest	No change (no data shown)	At rest	No change (no data shown)	0
Grimbert, 2004[25]	-	-	-	-	-	-	At rest	O: 94.4 (3.3)	At rest	O: 21.2 (8.4)	-
Harris-Eze, 1995[26]	-	-	On exertion (Emax)	No change (no data shown)	-	-	At rest and on exertion (Emax)	R: no change (no data shown) E-2.5 mg: 85 (7) E-5 mg: 85 (6) E-C: 84 (7)	At rest and on exertion (Emax)	R: no change (no data shown) E-2.5 mg: 40 (9) E-5 mg: 43 (11) E-C: 40 (12)	-
Hui, 2014[27]	-	-	-	-	-	-	At rest and on exertion (6MWT)	R-I: 96.5 (2.6); -0.6 (1.1)[b] R-C: 96.2 (1.9); +1.2 (2.1)[b] E-I: 96.8 (2.4); -1.2 (1.7)[b] E-C: 96.1 (1.9); +0.8 (2.7)[b]	At rest and on exertion (6MWT)	R-I: 18.2 (1.6); -0.6 (3.3)[b] R-C: 18.6 (1.6); 0 (1.1)[b] E-I: 21.0 (2.9); -2.4 (2.7)[a,b] E-C: 23.4 (3.9); -1.2 (3.9)[b]	-

Table S7. Continued

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD number *Definition*
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Jankelson, 1997[28]	-	-	-	-	-	-	On exertion (6MWT)	20 mg: 87.4 (6.6) 40 mg: 87.6 (6.2) C: 87.2 (4.6)	-	-	-
Jensen, 2012[29]	-	-	At rest and on exertion (CWRT)	R-I: 4.9 (0.5) R-C: 4.9 (0.6) E-I: 5.8 (1.0) E-C: 5.8 (1.0)	-	-	At rest and on exertion (CWRT)	R-I: 96.3 (1.7) R-C: 96.5 (1.4) E-I: 94.1 (3.1) I-C: 93.4 (6.6)	At rest and on exertion (CWRT)	R-I: 19.7 (4.2) R-C: 20.2 (4.2) E-I: 33.8 (5.5) E-C: 35.1 (4.5)	0
Johnson, 2002[30]	-	-	-	-	-	-	-	-	At rest	I: 21 (6) C: 21 (6)	-
Krajnik, 2009[31]	At rest, venous	No change (no data shown)	-	-	At rest, venous	No change (no data shown)	At rest	No change (no data shown)	-	-	-
Light, 1989[32]	At rest and on exertion (Emax), arterial	R-I: 4.9 (0.9) R-C: 4.7 (0.6) E-I: 5.6 (1.0) E-C: 5.1 (1.1)[c]	-	-	At rest and on exertion (Emax), arterial	R-I: 10.2 (1.6) R-C: 10.4 (1.9) E-I: 8.9 (1.5) E-C: 9.6 (2.1)[c]	At rest and on exertion (Emax)	R-I: 93.5 (3.2) R-C: 94.1 (3.1) E-I: 89.9 (6.4) E-C: 91.4 (6.3)[c]	At rest and on exertion (Emax)	R-I: 19.9 (4.2) R-C: 20.1 (1.7) E-I: 28.0 (4.8) E-C: 31.6 (6.1)	-
Light, 1996[33]	-	-	On exertion (Emax)	I: +0.1 (0.2)[b] C: -0.1 (0.2)[b]	-	-	-	-	-	-	-
Masood, 1995[34]	-	-	-	-	-	-	On exertion (Emax)	O: 93.7 (3.6)	On exertion (Emax)	O: 53.7 (17.4)	-

Table S7. Continued

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD number *Definition*
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Mazzocato, 1999[35]	-	-	-	-	-	-	At rest	I: 0 (1.5)[b] C: -0.8 (1.3)[b]	At rest	I: -2 (2.2)[b] C: 0 (1.7)[b,e]	0 *Difference in SaO_2*
Munck, 1990 (part 2)[36]	At rest, arterial	I: +0.2 (-0.3;0.8)[f] C: -0.1 (-0.7;1.3)[f]	-	-	At rest, arterial	I: -0.4 (-3.9;1.5)[f] C: -0.3 (-2.3;1.9)[f]	At rest	O: 0[g]	Excluded (no data shown)	-	-
Natalini, 2011[37]	At rest, arterial	PSV-I: 6.27 (1.9)[a] PSV-C: 5.9 (1.9)	-	-	At rest, arterial	PSV-I: 14.4 (13.2;19.7)[h]; -0.27 (-2.67;-1.33)[i] PSV-C: 12.0 (11.7;13.9)[h]; no cfb data shown	-	-	At rest	PSV-I: 19 (5)[a]; +8 (4;12)[i] PSV-C: 29 (27;30)[h]; no cfb data shown UB-I: 20 (18;23)[a,h]; +9 (6;13)[i] UB-C: 31 (5); no cfb data shown	-
Navigante, 2010[38]	-	-	-	-	-	-	At rest	FTP-I: 94.1 (3.7) FTP-C: 94.7 (2.9) FUP-I: 94.6 (2.8) FUP-C: 94.6 (3.1)	-	-	-
Noseda, 1997[39]	-	-	-	-	-	-	At rest	10 mg+O_2: 93 (6)[a] 20 mg+O_2: 94 (4)[a] 10 mg-O_2: 90 (8) C: 95 (4)[a]	At rest	10 mg+O_2: 17.9 (5.3) 20 mg+O_2: 19.1 (4.6) 10 mg-O_2: 19.0 (3.9) C: 19.1 (3.9)	-

Table S7. Continued

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	number *Definition*
Otulana, 2004 (phase 3)[40]	-	-	-	-	-	-	At rest	No change (no data shown)	At rest	No change (no data shown)	-
Oxberry, 2011[41]	-	-	-	-	-	-	At rest	1h-mor: -0.5 (1.7)[b] 1h-oxy: -0.2 (1.5)[b] 1h-C: -0.6 (1.6)[b] 4d-mor: -0.7 (2.0)[b] 4d-oxy: -0.5 (2.0)[b] 4d-C: -0.3 (1.7)[b]	At rest	1h-mor: -1.1 (1.7)[b] 1h-oxy: -1.6 (1.6)[b] 1h-C: -1.1 (2.0)[b] 4d-mor: -0.5 (2.7)[b] 4d-oxy: -1.6 (2.5)[b] 4d-con: -0.9 (2.7)[b]	-
Poole, 1998[42]	-	-	-	-	-	-	At rest	I: +0.3 (1.5)[b] C: +0.1 (0.9)[b]	-	-	-
Rice, 1987[43]	At rest, arterial	24h-I: 5.59 (0.6)[a] 24h-C: 5.45 (0.3) 1m-I: 5.45 (0.5)[a] 1m-C: 5.20 (0.8)	-	-	At rest, arterial	4h-I: 7.81 (1.5) 24h-C: 8.65 (1.5) 1m-I: 8.45 (1.5) 1m-C: 7.99 (1.3)	-	-	-	-	-
Robin, 1986[44]	At rest	No change (no data shown)	-	-	At rest	No change (no data shown)	-	-	-	-	-
Schonhofer, 1998[45]	At rest, capillary	I: 5.41 (0.6)[a,c] C: 4.88 (0.7)	-	-	At rest, capillary	I: 7.77 (0.7)[a,c] C: 8.24 (0.8)	-	-	-	-	0

Table S7. Continued

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD number *Definition*
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Shohrati, 2012[46]	-	-	-	-	-	-	-	-	At rest	I: -1.5 (1.1)[b,e] C: -0.1 (0.3)[b]	-
Smith, 2009[47]	-	-	-	-	-	-	At rest	No change (no data shown)	At rest	No change (no data shown)	-
Williams, 2003[48]	-	-	On exertion (Emax)	I: 5.2 (1.0) C: 5.1 (0.9)	-	-	-	-	On exertion (Emax)	I: 29 (4) C: 31 (8)	-
Woodcock, 1982[49]	At rest, arterial	30mg: 4.67 (0.5)[c] 60mg: 4.77 (0.4)[c] C: 4.42 (0.4)	-	-	At rest, arterial	30mg: 9.57 (0.7) 60mg: 9.35 (1.0) C: 9.45 (0.6)	-	-	-	-	-

Notes: Results are displayed as post-treatment scores (standard deviation) are presented, unless stated else. [a] significant different change between baseline and post-treatment; [b] mean change from baseline (standard deviation); [c] significant difference between post-treatment of intervention and control group; [d] trend for a difference; [e] significant different change between intervention and control group; [f] median change from baseline (range); [g] median change from baseline; [h] median post-treatment score (interquartile range) post-treatment scores; [i] median change from baseline (interquartile range) change from baseline. **Abbreviations:** C, change in control group; cfb, change from baseline; CWRT, constant work rate test; E, measured on exertion; Emax, maximal exercise test; I, change in intervention group; N, change in nebulized group; O, overall change (no specification of change in intervention and control group); $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; PSV, pressure support ventilation; R, measured at rest; RD, respiratory depression; RR, respiratory rate; S, change in systemic group; SaO_2, arterial oxygen saturation; UB, unassisted breathing.

Table S8. Results of nonrandomized trials

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD number *Definition*
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Allcroft, 2013[50]	-	-	At rest	No change (no data shown)	-	-	Excluded (baseline data only)		-	-	0
Boyd, 1997[51]	-	-	-	-	-	-	-	-	At rest	0	-
Bruera, 1990[52]	-	-	At rest	4.40 (1.2)	-	-	At rest	86 (11)	At rest	31 (9)	-
Bruera, 1993 (part 2)[19]	-	-	-	-	-	-	-	-	-	-	0
Clemens, 2007[53]	-	-	-	-	-	-	At rest	95 (4.0)	At rest	29 (5)[a]	0
Clemens, 2008.1[54]	At rest, transcutaneous	5.71 (0.7)	-	-	-	-	At rest	93.3 (2.8)	At rest	-29.0 (4.0)[a]	0 *Increase in $PaCO_2$*
Clemens, 2008.2[55]	At rest, transcutaneous	4.52 (0.8)	-	-	-	-	At rest	94.8 (4.0)	At rest	29.0 (3.1)[a]	0 *Increase in $PaCO_2$ >6.0 kPa or ≥0.5 kPa above baseline, decrease in RR < 10 breaths·minute^{-1} and decrease in SaO_2 < 90%*
Clemens, 2008.3[56]	At rest, transcutaneous	ON: 4.99 (8.8) PT: 4.52 (1.1)	-	-	-	-	At rest	ON: 95.1 (4.5) PT: 94.3 (3.7)	At rest	ON: 28.0 (3.0)[a] PT: 28.3 (3.1)[a]	0 *Increase in $PaCO_2$ >6.0 kPa or ≥0.5 kPa above baseline, decrease in RR < 10 breaths·minute^{-1} and decrease in SaO_2 < 90%*

Table S8. Continued

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD number *Definition*
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Clemens, 2009[57]	At rest, transcutaneous	Hypoxic/ON: 5.20 (0.7) Hypoxic/PT: 4.67 (1.2) Nonhypoxic/ ON: 5.07 (0.8) Nonhypoxic/ PT: 4.80 (0.8)	-	-	-	-	At rest	Hypoxic/ON: 91.0 (1.2)[a] Hypoxic/PT: 87.0 (6.0)[a] Nonhypoxic/ ON: 95.0 (3.5) Nonhypoxic/ PT: 95.0 (3.0)	At rest	Hypoxic/ON: 24.5 (4.4)[a] Hypoxic/PT: 26.3 (4.6)[a] Nonhypoxic/ ON: 27.0 (4.0)[a] Nonhypoxic/ PT: 27.0 (3.4)[a]	0 *Increase in $PaCO_2$ >6.0 kPa or ≥0.5 kPa above baseline, decrease in RR < 10 breaths·minute^{-1} and decrease in SaO_2 < 90%*
Clemens, 2011[58]	At rest, transcutaneous	5.03 (0.7)	-	-	-	-	At rest	95.2 (3.5)	At rest	32.0 (4.0)[a]	0 *Increase in $PaCO_2$ >6.0 kPa or ≥0.5 kPa above baseline, decrease in RR < 10 breaths·minute^{-1} and decrease in SaO_2 < 90%*
Cohen, 1991[59]	At rest, unclear place of measurement	Increase (no data shown)	-	-	At rest, unclear place of measurement	Increase in patients with PaO_2 <8.0 kPa; decrease in patients with PaO_2 >8.0 kPa (no data shown)	-	-	At rest	Fluctuation in RR; only in 1 patient the RR fell below 10 breaths·minute^{-1} (no data shown)	-
Coyne, 2002[60]	-	-	-	-	-	-	At rest	96.7 (1.2)[a]	At rest	24.1 (1.7)[a]	-
Currow, 2011[61]	-	-	-	-	-	-	-	-	-	-	0
Gauna, 2008[62]	-	-	-	-	-	-	At rest	95.3 (3.2)	At rest	22.6 (5.5)[a]	-

Table S8. Continued

First author, year	$PaCO_2$ (kPa)		$P_{ET}CO_2$ (kPa)		PaO_2 (kPa)		SaO_2 (%)		RR (breaths·minute^{-1})		RD number *Definition*
	Measure	Result	Measure	Result	Measure	Result	Measure	Result	Measure	Result	
Munck, 1990 (part 1)[36]	At rest, arterial	No change (no data shown)	-	-	At rest, arterial	No change (baseline data only)	At rest	SaO_2 declined temporarily from 93% to 92% after 1 hour on day 2 (120 mg)[a]	At rest	No change (no data shown	0
Otulana, 2004 (phase 4)[40]	-	-	-	-	-	-	-	-	At rest	No change (no data shown)	-
Tanaka, 1999[63]	-	-	-	-	-	-	At rest	No change (no data shown)	At rest	No change (no data shown)	0 *Decrease in RR > 10% and reduction of SaO_2 > 5.*

Notes: Results are displayed as post-treatment scores (standard deviation) are presented, unless stated else. [a] significant change from baseline. **Abbreviations:** ON, opioid-naïve; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of oxygen; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; PT, pre-treated; RD, respiratory depression; RR, respiratory rate; SaO_2, arterial oxygen saturation.

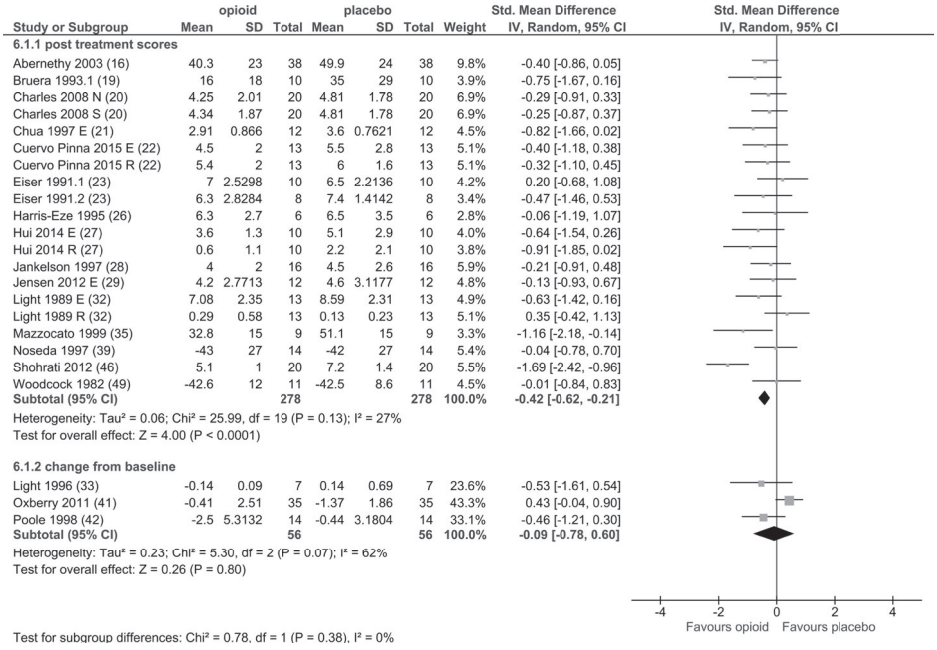

Figure S1. Effect of opioid treatment in patients with advanced disease on breathlessness.
Abbreviations: E, measured on exertion; N, nebulized administration; R, measured at rest; S, systemic administration.

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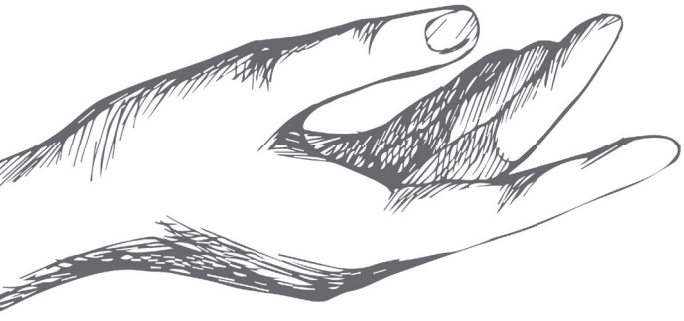

CHAPTER 3

Healthcare and societal costs in patients with COPD and breathlessness after completion of a comprehensive rehabilitation program

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Abstract

Breathlessness is one of the most frequent symptoms in chronic obstructive pulmonary disease (COPD). COPD may result in disability, decreased productivity and increased healthcare costs. The presence of comorbidities increases healthcare utilization. However, the impact of breathlessness burden on healthcare utilization and daily activities is unclear. This study's goal was to analyze the impact of breathlessness burden on healthcare and societal costs. In this observational single-center study, patients with COPD were followed-up for 24 months after completion of a comprehensive pulmonary rehabilitation program. Every three months participants completed a cost questionnaire, covering healthcare utilization and impact on daily activities. The results were compared between participants with low (modified Medical Research Council [mMRC] grade <2; LBB) and high baseline breathlessness burden (mMRC grade ≥2; HBB). Healthcare costs in year 1 were €7302 (95% confidence interval €6476-€8258) for participants with LBB and €10,738 (€9141-€12,708) for participants with HBB. In year 2, costs were €8830 (€7372-€10,562) and €14,933 (€12,041-€18,520), respectively. Main cost drivers were hospitalizations, contact with other healthcare professionals and rehabilitation. Costs outside the healthcare sector in year 1 were €682 (€520-€900) for participants with LBB and €1520 (€1210-€1947) for participants with HBB. In year 2, costs were €829 (€662-€1046) and €1457 (€1126-€1821), respectively. HBB in patients with COPD is associated with higher healthcare and societal costs, which increases over time. This study highlights the relevance of reducing costs with adequate breathlessness relief. When conventional approaches fail to improve breathlessness, a personalized holistic approach is warranted.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic disease that is characterized by persistent reduction of airflow and respiratory symptoms.[1] The worldwide prevalence of COPD was estimated at 3.9% in 2017,[2] and annually about three million people die because of COPD.[3] The prevalence of COPD is expected to increase globally in the coming years due to higher smoking prevalence in low-income countries and ageing of the population.[4]

The most frequently reported symptoms of COPD are breathlessness, coughing and fatigue.[5] Disease severity is determined using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification.[1] Within this classification, the modified Medical Research Council (mMRC) scale[6] and COPD Assessment Test (CAT)[7,8] are used to measure symptom burden. Low breathlessness burden is represented by a mMRC grade of 0 or 1 point and high breathlessness burden by a mMRC grade of ≥2 points; low health status is represented by a CAT score of <10 points and high health status by a CAT score of ≥10 points.[1]

COPD may result in disability, decreased productivity and increased health-related costs.[1] In COPD, exacerbations and hospital admissions account for the largest component of health-related costs.[9-11] With increasing disease severity, healthcare utilization increases.[9,11,12] Furthermore, healthcare costs increase with the presence of comorbidities.[9] Next to the healthcare costs, COPD has a major impact on society.[13] In 2017, COPD was the sixth leading cause of loss in disability-adjusted life years for women and ninth leading cause for men worldwide.[14] With increasing disease severity, there is impact on workplace and home productivity and on the burden for relatives.[9,10,13]

Current knowledge on the impact of disease severity and breathlessness burden on healthcare utilization and costs is based on retrospective claims data[9,12] or patient data recalling 12 months.[10] The goal of this study was to prospectively analyze the impact of breathlessness burden in COPD, assessed by the mMRC scale, on societal costs over a follow-up period of 24 months after completion of a comprehensive pulmonary rehabilitation (PR) program.

Methods

Study design

This was a secondary analysis of the CIRO CO-morbidity (CIROCO) study, an observational single-center study to identify biomarkers, comorbidities, increased healthcare costs and poor prognosis in patients with COPD. The methodology of the CIROCO study has been described in detail elsewhere.[15] For the current analysis, data of the PR program were left aside. The baseline assessment for this analysis was therefore the final assessment of the PR program. Participants were recruited between November 2007 and November 2010. All subjects provided written informed consent. The study was approved by the local medical ethics committee (MEC 10-3-067) and conducted in accordance with the Declaration of Helsinki.
For the current analysis, a societal perspective was adopted including healthcare costs and costs outside the healthcare sector.

Participants

Patients were eligible to participate in the CIROCO study if they were diagnosed with moderate to very severe COPD (GOLD grades II–IV), smoked at least 10 pack-years and were aged between 40 and 80 years. For the current analysis, participants had to have completed an 8-week inpatient (5 days/week) or 14-week outpatient (3 days/week) comprehensive PR program at CIRO in Horn, The Netherlands and at least one visit during the follow-up. Exclusion criteria were described in detail elsewhere.[15]

Assessments and questionnaires

Baseline measurements

At baseline, participants underwent a two-day assessment at the end of the PR program, during which data were collected on demographics, smoking status, number of exacerbations and hospital admissions in the past 12 months, lung function, comorbidities using the Charlson Comorbidity Index (CCI)[16] and mMRC grade.[6]

Follow-up

During a follow-up of 24 months, participants completed the mMRC breathlessness scale and a cost questionnaire (Supplemental Methods 1) every three months during a phone call. The mMRC breathlessness scale assesses the perceived disability of breathlessness in activities of daily living. The scale consists of five grades (grade 0: '*breathless only with strenuous exercise*'; grade 4: '*too breathless to leave the house or breathless when dressing*').[6] The cost questionnaire covered healthcare utilization, employment status at baseline, inability to perform daily activities (employed and/or household work of both participants and informal caregivers) and long-term sick leave. Healthcare utilization included contact with healthcare professionals, hospitalization, respiratory tests and use of long-term oxygen therapy (LTOT). For all

questions, the reason (breathing problems or other health problems) and number of times or number of days were collected. Furthermore, prescribed and over-the-counter medication use was discussed. At the end of the follow-up, information on participation in a second PR program was collected from the patient file and prescribed medication use was checked using medication lists.
To be able to calculate healthcare costs, several assumptions about exacerbations and hospital admissions, medication use and use of LTOT were made. These are described in Supplemental Methods 2.

Healthcare costs
For valuation of healthcare resource use, reference prices were obtained from the cost manual of the Dutch National Healthcare Institute[17] and indexed to July 2019. For the reference prices not stated in the cost manual, the rate list first-line diagnostics of the Dutch Healthcare Authority[18] was used. Prescribed medication was valued using medication prices of July 2019 from the medication database by the Dutch National Healthcare Institute.[19] Prices of medication that were not on the market anymore were extracted from the Farmacotherapeutisch Kompas 2008 and indexed to July 2019. Delivery costs by the pharmacist were accounted for medication within the drug reimbursement system. For the base-case analysis, the lowest medication price was used.[17] A sensitivity analysis using the highest medication price was conducted.

Costs outside healthcare sector
Information on employment status was only collected at baseline of the CIROCO study. Data collection regarding impact on daily activities did not distinguish between household activities or paid work. Therefore, in the base-case analysis impact on daily activities for both participants and informal caregivers was conservatively valued as household work. In a sensitivity analysis, impact on daily activities for the subgroup of participants that were employed at baseline was valued using the friction cost method.[17] Impact on daily activities for the other participants was still valued as household work. In another sensitivity analysis, impact on daily activities of informal caregivers was excluded from the analysis. Over-the-counter medication was valued using medication prices of July 2019 from the medication database by the Dutch National Healthcare Institute.[19] Data on transportation to healthcare professionals or the hospital were not collected. Based on the mean distance to healthcare professionals or the hospital, transportation by car and reference prices from the cost manual,[17] costs for transportation were calculated.

Statistical analysis
Analyses were performed using SPSS statistics version 25.0 (IBM Corp, Armonk, NY). Participant characteristics, healthcare utilization and impact on daily activities were described as mean (SD) for continuous variables and number (percentage)

for categorical variables. Cost data of the first and second year were presented as mean (95% bootstrapped bias-corrected and accelerated confidence interval; 95% BCa CI). Cost data for the second year were discounted with 4%, according to the Dutch cost manual.[17] Comparison between the years was performed using Wilcoxon signed rank tests.

Baseline mMRC grades were used to compose two breathlessness burden profiles. Participants with low breathlessness burden reported a mMRC grade of <2 points at start of the follow-up, and participants with high breathlessness burden reported a mMRC grade of ≥2 points at start of the follow-up, according to the GOLD classification.[1] Differences in baseline characteristics, healthcare utilization or impact on daily activities between the groups with low and high breathlessness burden were analyzed using independent samples T-tests or Mann-Whitney U tests, according to data distribution. Differences in healthcare utilization or impact on daily activities within breathlessness burden groups between breathing and other health problems were analyzed using dependent samples T-tests or Wilcoxon signed rank tests, according to data distribution. Categorical data were analyzed using χ^2-tests. Correlation between continuous parameters was analyzed using Pearson or Spearman correlation coefficient, according to data distribution. Missing data were imputed using single imputation on means because of the minimal amount of missing data.

Results

Participants

Of the 213 participants included in the CIROCO study, data of 178 was included in the current analysis (Figure 1). A total of 350 patient years was collected, 2.0 (0.2) years per participant. The total population was aged 63.6 (7.0) years and 60.1% was male. Participants not included in the analysis withdrew consent, deceased, dropped-out because of physical or mental inability to complete the study before the first follow-up visit or missed an mMRC grade at baseline (Figure 1). Participants not included in the analysis were comparable to participants included in the analysis, except for smoking status: participants not included were more often smoker (44.1% vs. 19.1%; p=0.002).

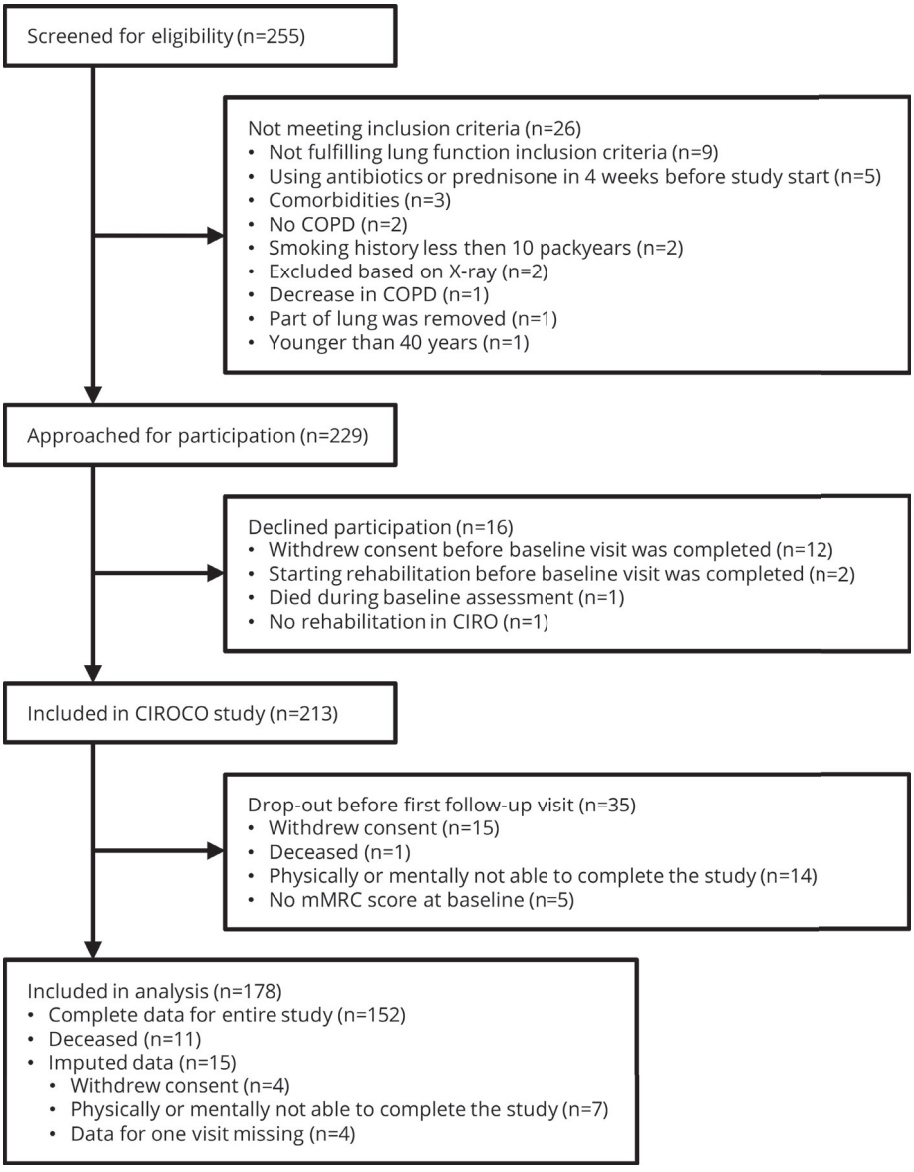

Figure 1. Flow chart

Breathlessness burden

Before the PR program 59 participants (33.1%) experienced low breathlessness burden, and 119 participants (66.9%) experienced high breathlessness burden. During PR, in 10 participants breathlessness burden changed from low to high breathlessness burden and in 33 participants from high to low breathlessness burden. After the PR program, so at baseline of these analyses, 82 participants (46.1%)

experienced low breathlessness burden, and 96 participants (53.9%) experienced high breathlessness burden. Participants with low and high breathlessness burden were similar at baseline, except for number of exacerbations in the previous 12 months, CCI and FEV_1 (Table 1). Breathlessness burden during follow-up is shown in Supplemental Table S1.

Table 1. Baseline characteristics of total study population and participants with low and high breathlessness burden.

	Total group (n=178)	Low breathlessness burden (n=82)	High breathlessness burden (n=96)	p-value[a]
Age (years)	63.6 ± 7.0	62.8 ± 7.6	64.2 ± 6.4	0.183
Male, n (%)	107 (60.1)	48 (58.5)	59 (61.5)	0.692
BMI (kg/m^2)	26.7 ± 5.4	26.5 ± 4.4	27.0 ± 6.1	0.821
Smoking status, n (%)				0.161
Ex-smoker	144 (80.9)	70 (85.4)	74 (77.1)	
Smoker	34 (19.1)	12 (14.6)	22 (22.9)	
Exacerbations in <12 months (n)	1.4 ± 1.6	0.9 ± 1.2	1.8 ± 1.9	**0.002**
Hospital admissions in <12 months (n)	0.5 ± 1.1	0.4 ± 0.9	0.6 ± 1.2	0.206
CCI (points)	1.6 ± 0.9	1.4 ± 0.7	1.8 ± 1.0	**0.007**
FEV_1, (l)	1.42 ± 0.56	1.56 ± 0.54	1.30 ± 0.54	**<0.001**

Notes: Data are shown as mean ± SD. Significance testing was performed using Mann-Whitney U tests or χ^2 tests, as appropriate. [a] significant p-values are shown in bold. **Abbreviations:** BMI, Body Mass Index; CCI, Charlson Comorbidity Index; FEV_1, forced expiratory volume in 1 s.

Employment status

Ten participants (5.6%) were employed full-time at baseline (seven with low breathlessness burden and three with high breathlessness burden) and were working 39.9 (6.8) hours/week. Eight participants (4.5%) were employed part-time (seven with low breathlessness burden and one with high breathlessness burden) and were working 25.8 (5.4) hours/week. Another four participants (2.2%) were employed, but the amount of hours is unknown. 26 participants (14.6%) were on long-term sick leave for a period of 7.5 (7.8) months. Reasons for long-term sick leave were breathing problems (50.0%), other health problems (15.4%), breathing and other health problems (3.8%) or unknown (30.8%). 14 participants (7.9%) were incapacitated for work. The other participants were retired (87, 48.9%), house-person (25, 14.0%) or unemployed (4, 2.2%).

Healthcare costs

Outpatient care

During the follow-up, all participants visited a healthcare professional for breathing problems as well as other health problems. The family doctor and medical specialist were visited more often by participants with high breathlessness burden compared to participants with low breathlessness burden (p=0.015 and p=0.042, respectively), while other healthcare professionals (including, but not limited to physiotherapists, occupational therapists and nurses) were visited equally often (p=0.152; Table 2). In the majority of cases, visits were more often for breathing problems than for other health problems (Table 2).

In the first year, costs for outpatient care for participants with low breathlessness burden were €3527 and for participants with high breathlessness burden €3792. In the second year, these costs were €3634 and €4166, respectively. Costs did not differ between groups (Table 3 and Supplemental Table S2) or years (Table 3).

Inpatient care

Participants with high breathlessness burden more often needed inpatient care compared to participants with low breathlessness burden (71.9% vs. 57.3%; p=0.042). Especially, participants with high breathlessness burden more often visited the emergency room or were more often hospitalized compared to participants with low breathlessness burden (p=0.016 and p=0.005, respectively; Table 2). In the majority of cases, contacts were more often for breathing problems than for other health problems (Table 2).

In the first year, costs for inpatient care were €1606 for participants with low breathlessness burden and €3934 for patients with high breathlessness burden. In the second year, these costs were €1876 and €3910, respectively. Costs for participants with high breathlessness burden were higher in both years (Table 3 and Supplemental Table S2). Costs did not differ between the years (Table 3).

Diagnostics

The number of participants that underwent a respiratory test (including spirometry test, advanced pulmonary test, plain chest X-ray and chest computer tomography) and the number of tests were similar for participants with low and high breathlessness burden (p=0.619 and p=0.199, respectively; Table 2). Costs for pulmonary tests were similar for participants with low and high breathlessness burden in the first year (€191 and €240 per participant, respectively) and second year (€274 and €311 per participant, respectively; Table 3 and Supplemental Table S2).

Table 2. Healthcare and non-healthcare utilization per participant per year.

	Low breathlessness burden (n=82; 46.1%)				High breathlessness burden (n=96; 53.9%)				
	Total	Breathing problems	Other health problems	p-value[a]	Total	Breathing problems	Other health problems	p-value[a]	p-value[a]
Outpatient care									
% user	100.0	100.0	100.0	1.000	100.0	100.0	100.0	1.000	1.000
Total number of visits	96.5 (35.0)	85.0 (32.2)	11.5 (12.6)	**<0.001**	111.1 (55.7)	95.8 (49.5)	14.2 (18.2)	**<0.001**	0.060
Family doctor	8.9 (5.1)	4.2 (3.7)	4.8 (3.4)	0.204	12.3 (9.3)	7.1 (6.7)	5.2 (4.5)	**0.039**	**0.015**
Medical specialist	6.4 (5.8)	3.8 (4.0)	2.6 (4.1)	**0.004**	7.0 (4.8)	4.5 (4.1)	2.6 (2.6)	**<0.001**	**0.042**
Other healthcare professional	81.2 (33.5)	77.1 (31.5)	4.1 (9.7)	**<0.001**	90.8 (53.3)	84.3 (48.8)	6.5 (14.7)	**<0.001**	0.152
Inpatient care									
% user	57.3	42.7	32.9	0.216	71.9	64.6	35.4	**<0.001**	**0.042**
Ambulance transportation	0.20 (0.60)	0.16 (0.59)	0.04 (0.13)	**0.027**	0.34 (0.75)	0.26 (0.73)	0.07 (0.22)	**0.009**	0.145
Visit to emergency room	0.37 (0.58)	0.21 (0.44)	0.16 (0.34)	0.477	0.67 (0.96)	0.51 (0.84)	0.16 (0.36)	**<0.001**	**0.016**
Hospitalizations	0.51 (0.78)	0.34 (0.63)	0.17 (0.36)	**0.023**	1.16 (1.71)	0.73 (1.24)	0.43 (1.18)	**0.001**	**0.005**
Diagnostics									
% user	-	96.3	-	-	-	94.8	-	-	0.619
Respiratory tests	-	3.0 (1.9)	-	-	-	3.7 (2.7)	-	-	0.199
Medication									
Number of prescribed medications	25.7 (13.1)	13.0 (10.1)	12.7 (6.6)	0.590	33.1 (18.7)	19.0 (14.1)	14.1 (7.5)	**0.003**	**0.009**
% short-acting bronchodilators	-	61.0	-	-	-	82.3	-	-	**0.002**
% long-acting bronchodilators	-	98.8	-	-	-	100.0	-	-	0.287
% inhaled corticosteroids	-	89.0	-	-	-	94.8	-	-	0.154
% systemic corticosteroids[b]	75.6	69.5	17.1	**<0.001**	85.4	84.4	24.0	**<0.001**	0.097
% antibiotics	85.4	76.8	42.7	**<0.001**	84.4	80.2	29.2	**<0.001**	0.854
% influenza vaccination	-	93.9	-	-	-	88.5	-	-	0.213
% cardiac medication	-	-	59.8	-	-	-	71.9	-	0.088
% strong opioids[c]	7.3	1.2	7.3	0.063	11.5	4.2	8.3	0.344	0.349

Table 2. Continued

	Low breathlessness burden (n=82; 46.1%)				High breathlessness burden (n=96; 53.9%)				
	Total	**Breathing problems**	**Other health problems**	**p-value[a]**	**Total**	**Breathing problems**	**Other health problems**	**p-value[a]**	**p-value[a]**
LTOT									
% user	-	39.0	-	-	-	54.2	-	-	**0.044**
LTOT[d]	-	23.5 (18.8)	-	-	-	28.3 (17.0)	-	-	0.159
Inability of participant to perform daily activities									
% that was unable	90.2	82.9	46.3	**<0.001**	99.0	97.9	56.3	**<0.001**	**0.008**
Days of inability	30.0 (42.9)	21.5 (8.8)	8.6 (18.2)	**<0.001**	75.5 (84.2)	64.6 (83.4)	10.9 (20.9)	**<0.001**	**<0.001**
Inability of informal caregiver to perform daily activities									
% that was unable	18.3	14.6	6.1	0.092	30.2	27.1	12.5	**0.003**	0.066
Days of inability	3.1 (11.2)	2.7 (10.9)	0.4 (1.8)	0.094	8.1 (34.9)	7.8 (34.8)	0.3 (1.6)	**<0.001**	0.064

Notes: Data are shown as mean (SD). Significance testing was performed using Mann-Whitney U tests, Wilcoxon signed rank tests or $\chi 2$ tests, as appropriate. [a] Significant p-values are shown in bold. [b] Use of both continuous and intermittent systemic corticosteroids. [c] Strong opioids include: fentanyl, morphine, oxycodone and piritramide. [d] Only considering participants that used LTOT. **Abbreviations:** LTOT, long-term oxygen therapy.

Table 3. Mean costs per participant per year (in Euro's).

	Low breathlessness burden (n=82; 46,1%)			High breathlessness burden (n=96; 53.9%)		
	Year 1	**Year 2**	**p-value[a]**	**Year 1**	**Year 2**	**p-value[a]**
Healthcare costs						
Outpatient	3527	3634	0.844	3792	4166	0.200
Inpatient	1606	1876	0.672	3934	3910	0.776
Diagnostics	191	274	0.113	240	311	0.128
Rehabilitation[b]	16,174[c]	17,625	0.173	12,338[d]	21,109	**0.008**
Prescribed medication	1616	1772	**0.008**	1867	2028	0.114
LTOT[e]	566	713	0.199	629	681	**0.020**
Subtotal healthcare costs	7302	8830	0.507	10,738	14,933	**0.012**
Costs outside healthcare sector						
Impact daily activities participant	339	493	0.485	1153	963	0.553
Impact daily activities informal caregiver	49	27	0.280	23	204	**0.001**
Transportation	105	98	0.172	102	109	0.210
Over-the-counter medication	189	212	0.137	242	181	**0.027**
Subtotal costs outside healthcare sector	682	829	0.335	1520	1457	0.556
Total societal costs	7985	9660	0.441	12,258	16,390	0.059

Notes: Data are shown as mean. [a] Significant p-values are shown in bold. [b] Only considering participants that underwent rehabilitation. [c] Only one participant with low breathlessness burden was admitted to pulmonary rehabilitation in year 1, so no confidence interval could be calculated. [d] Some or all bootstrap sample results are missing, so no bootstrap estimation has been performed. [e] Only considering participants that used LTOT.
Abbreviations: LTOT, long-term oxygen therapy.

Pulmonary rehabilitation

Within the two years, 30 participants were again admitted to the assessment prior to a comprehensive PR program. In the first year, 1/82 (1.2%) participants with low breathlessness burden and 5/96 (5.2%) participants with high breathlessness burden were re-admitted (p=0.142). In the second year, 5/82 (6.1%) participants with low breathlessness burden and 19/96 (19.8%) participants with high breathlessness burden were re-admitted (p=0.008). In total nine participants only completed the baseline assessment, and 21 participants started the PR program (five with low breathlessness burden and 16 with high breathlessness burden). Costs for PR were €12,977 per participant for the first year and €20,383 per participant for the second year, only taking into account the participants who attended PR. Per year, costs for participants with low or high breathlessness burden were not different (Table 3 and Supplemental Table S2). Rehabilitation costs for patients with high breathlessness burden were higher in the second year compared to the first year (p=0.008; Table 3).

Prescribed medication

A total of 5291 medication prescriptions within the drug reimbursement system were registered, 2890 for respiratory diseases and 2401 for other diseases. This equals 16.2 prescriptions for respiratory medication and 13.5 prescriptions for other medication per participant (p=0.056). Participants with high breathlessness burden used significantly more respiratory medication compared to other medication (19.0 vs. 14.1, p=0.003), which was not the case for participants with low breathlessness burden (13.0 vs. 12.7, p=0.590; Table 2).

At baseline, 97.2% of participants was treated with a long-acting bronchodilator, 86.5% was treated with a short-acting bronchodilator, and 91.6% was treated with an inhaled corticosteroid (ICS). The frequency of use of medication for participants with low and high breathlessness burden during the follow-up is presented in Table 2. The use of short-acting bronchodilators was higher for participants with high breathlessness burden compared to participants with low breathlessness burden (82.3% vs. 61.0%, p=0.002). All other types of medication were used equally often by participants with low and high breathlessness burden (Table 2).

In the first year, medication costs were €1616 for participants with low breathlessness burden and €1867 for patients with high breathlessness burden (p=0.008; Table 3). In the second year, these costs were €1772 and €2028, respectively (p=0.114; Table 3). Costs did not differ between groups (Table 3 and Supplemental Table S2).

Long-term oxygen therapy

LTOT was used by 84 participants for on average 26.4 (17.7) weeks per participant per year. 32/82 (39.0%) participants with low breathlessness burden and 52/96 (54.2%) participants with high breathlessness burden used LTOT (p=0.044; Table 2). Costs per participant were not different for both groups, taking into account only the participants that used LTOT (€566 vs. €629 for the first year and €713 vs. €681 for the second year; Table 3 and Supplemental Table S2). Costs for participants with high breathlessness burden were higher in the second year compared to the first year (p=0.020; Table 3).

Costs per subgroup

Total healthcare costs in the first year were €9155 per participant and in the second year €12,122 per participant (Figure 2). In the first year costs of participants with low breathlessness burden were lower (€7302) compared with participants with high breathlessness burden (€10,738; Table 3 and Supplemental Table S2). Also, in the second year, costs of participants with low breathlessness burden were lower (€8830) than costs of participants with high breathlessness burden (€14,933; Table 3 and Supplemental Table S2). Costs for participants with high breathlessness burden and for the total study population were higher in the second year compared to the first year (Figure 2 and Table 3).

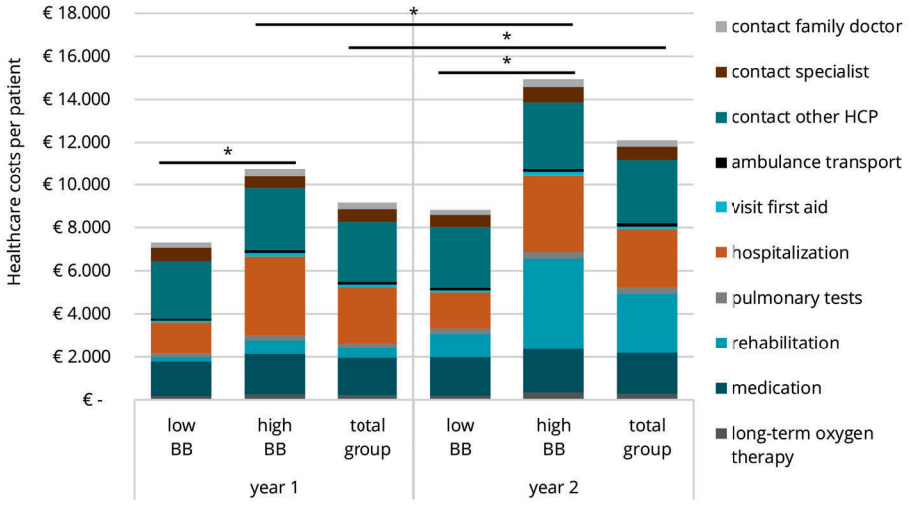

Figure 2. Healthcare costs per participant per year.
Notes: * Significant difference. **Abbreviations:** BB, breathlessness burden; HCP, health care professional.

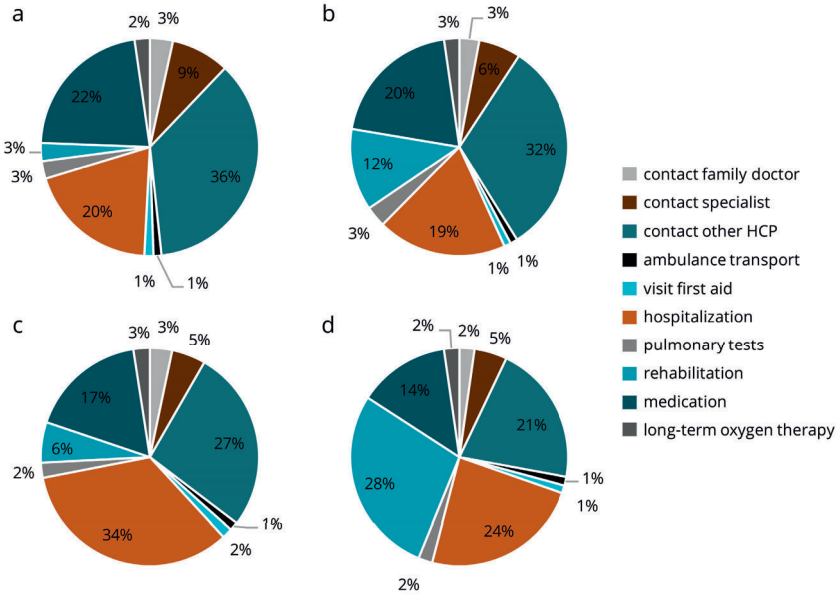

Figure 3. Cost components of healthcare resource use. (A) Patients with low breathlessness burden in year 1; (B) Patients with low breathlessness burden in year 2; (C) Patients with high breathlessness burden in year 1; (D) Patients with high breathlessness burden in year 2.

For participants with low breathlessness burden, the largest cost components were contacts with other healthcare professionals (36% in year 1 and 32% in year 2), medication (22% in year 1 and 20% in year 2) and hospitalizations (20% in year 1 and 19% in year 2; Figure 3). For participants with high breathlessness burden, the largest cost components differed per year. For year 1, these were hospitalizations (34%), contact with other healthcare professionals (27%) and medication (17%), while for year 2 these were rehabilitation (28%), hospitalization (24%) and contact with other healthcare professionals (21%; Figure 3).

Costs outside the healthcare sector

Impact on daily activities

About 90.2% of participants with low breathlessness burden and 99.0% of participants with high breathlessness burden was unable to perform daily activities during the two years of follow-up (p=0.008; Table 2). Participants with low breathlessness burden were unable to perform daily activities on 30.0 (42.9) days, while participants with high breathlessness burden were unable to perform daily activities on 75.5 (84.2) days (p<0.001; Table 2). For participants with low breathlessness burden, the costs were €339 per participant in year 1 and €493 per participant in year 2 (p=0.485), while for participants with high breathlessness burden the costs were €1153 per participant in year 1 and €963 per participant in year 2 (p=0.553; Table 3 and Supplemental Table S2). For both groups, inability was more often due to breathing problems than other health problems (Table 2).

About 18.3% of informal caregivers of participants with low breathlessness burden and 30.2% of informal caregivers of participants with high breathlessness burden had to interrupt their daily activities to take care of the participants (p=0.066; Table 2). This was on 3.1 and 8.1 days per participant per year, respectively (p=0.064). Costs were €49 in the first year and €27 in the second year for informal caregivers of participants with low breathlessness burden (p=0.280) and €23 in the first year and €204 in the second year for informal caregivers of participants with high breathlessness burden (p=0.001; Table 3 and Supplemental Table S2).

Over-the-counter medication

A total of 286 over-the-counter medications were registered, 113 for respiratory disease and 173 for other diseases (p=0.004). The number of medications per participant was equal for participants with low and high breathlessness burden (1.4 vs. 1.8, p=0.137).

Over-the-counter medication costs per participant were €189 for low breathlessness burden and €242 for high breathlessness burden in the first year and €212 for low breathlessness burden and €181 for high breathlessness burden in the second year (Table 3 and Supplemental Table S2). Costs for participants with high breathlessness burden were higher in year 1 compared to year 2 (p=0.027; Table 3).

Transportation
Annual transportation costs were €101 per participant for low breathlessness burden and €105 per participant for high breathlessness burden. Transportation costs in both groups were not different for the first and second year (Table 3 and Supplemental Table S2).

Total societal costs
Total societal costs differed between participants with low and high breathlessness burden in both years (Table 3 and Supplemental Table S2). Costs of participants with low breathlessness burden amounted €7985 in the first year and €9660 in the second year, while costs of participants with high breathlessness burden were €12,258 in the first year and €16,390 in the second year. There was no difference between the years (Table 3).
Healthcare costs were weakly correlated with FEV_1, both for low breathlessness burden (Spearman ρ −0.103, p=0.357 for year 1 and Spearman ρ −0.241, p=0.029 for year 2) and for high breathlessness burden (Spearman ρ −0.061, p=0.555 for year 1 and Spearman ρ −0.067, p=0.515 for year 2). For societal costs, the correlations were similar (low breathlessness burden year 1: Spearman ρ −0.119, p=0.288; high breathlessness burden year 1: Spearman ρ −0.080, p=0.438; low breathlessness burden year 2: Spearman ρ −0.224, p=0.043; high breathlessness burden year 2: Spearman ρ −0.095, p=0.358).

Sensitivity analysis
Table 4 and Supplemental Table S3 show the results of the sensitivity analyses. None of the analyses influenced the total societal costs to such extent that conclusions were altered, in both years costs for participants with high breathlessness burden were higher compared to costs of participants with low breathlessness burden. In the scenario of highest medication prices, the costs for participants with high breathlessness burden were higher in the second year compared to the first year (p=0.035), while in the other scenarios there was only a trend (Table 4).
Furthermore, scenarios with lowest costs and scenarios with highest costs were combined. The scenario with lowest costs equals the scenario in which impact on daily activities of informal caregivers was excluded. The scenario with highest costs included highest medication prices and valuing impact on daily activities of participants based on baseline employment status. Both scenarios had no influence on the differences between the groups, while in the scenario with the highest costs the costs for participants with high breathlessness burden were higher in the second year compared to the first year (p=0.030; Table 4).

Table 4. Results of sensitivity analyses on total societal costs per participant per year (in Euro's).

	Low breathlessness burden (n=82; 46,1%)			High breathlessness burden (n=96; 53.9%)		
	Year 1	Year 2	p-value[a]	Year 1	Year 2	p-value[a]
Base-case						
Total societal costs	7985	9660	0.441	12,258	16,390	0.059
Highest medication prices						
Total societal costs	9099	10,709	0.266	13,359	17,779	**0.035**
Impact on daily activities participant according to baseline employment status						
Total societal costs	8422	10,144	0.487	12,536	16,735	0.052
Impact on daily activities informal caregiver excluded						
Total societal costs	7936	9632	0.443	12,235	16,186	0.072
Combining all scenario's with highest costs						
Total societal costs	9536	11,193	0.347	13,637	18,124	**0.030**

Notes: Data are shown as mean. [a] Significant p-values are shown in bold.

Discussion

The CIROCO study provided an overview of healthcare and non-healthcare resource utilization and costs of patients with COPD who completed a comprehensive PR program during two years. This secondary analysis showed that high breathlessness burden in COPD patients is associated with high healthcare and non-healthcare costs. Total annual societal costs of participants with low breathlessness burden (mMRC<2) were €7985 (€7047-€9087) in year 1 and €9660 (€8045-€11,537) in year 2 vs. €12,258 (€10,573-€14,321) in year 1 and €16,390 (€13,255-€19,865) in year 2 for participants with high breathlessness burden. The difference between low and high breathlessness burden applied to almost all cost categories, except for outpatient care, diagnostics and medication.

Hospitalization, medication and contact with other healthcare professionals were the main cost drivers in this study. Previous cost analyses have shown similar results for hospitalization and medication.[9-13,20,21] The large contribution of contact with other healthcare professionals can be explained by the inclusion of participants immediately after completing a PR program. Although not registered, it can be assumed that the vast majority of the reported visits was with the physiotherapist. These patients are encouraged to continue training with a physiotherapist to retain the results of the PR program.
Patients with advanced COPD often have multimorbidity and experience multiple symptoms.[22] The current results show that medical specialists are consulted mainly for breathing problems, and these visits are probably more on a scheduled basis,

given the results that medical specialists are visited almost equally often by patients with low and high breathlessness burden. Family doctors are consulted for all kinds and more emergent problems, since they are visited almost equally often for breathing and other health problems, but more often by patients with high breathlessness burden than by patients with low breathlessness burden.
Almost as many respiratory tests were performed as visits to the chest physician. Furthermore, standard treatment with long-acting bronchodilators and inhaled corticosteroids is used by almost all participants. Participants with high breathlessness burden subsequently use short-acting bronchodilators as attempt to minimize symptoms. When these attempts fail, a new PR program is considered, given the results that significantly more patients with high breathlessness burden attend a PR program in the second year compared to the first year. Furthermore, PR programs in the second year are more often inpatient, leading to higher costs. This makes the PR program the largest cost component for this group in the second year. Breathlessness burden appears not to be a strong predictor of specialist visit frequency, deployed diagnostics or costs of applied pharmacological treatment. However, it can be assumed that this patient group requires another management approach. Given the multifactorial nature of breathlessness, a holistic approach should be considered.[23,24] When patients still experience severe breathlessness burden in daily life after completion of a comprehensive PR program, more focus should be on palliation of their breathlessness. This is emphasized by clinical practice guidelines.[25,26] Opioids have an important place in palliation of refractory breathlessness,[27] but results of the current study show that only 4.2% of patients with high breathlessness burden uses opioids for breathing problems. In a Swedish study observing patients with COPD needing LTOT, a similar low prescription rate was shown.[28]

Costs outside the healthcare sector only comprised 8.6% of total societal costs for participants with low breathlessness burden and 10.4% for participants with high breathlessness burden. This is much lower compared to other studies including patients with COPD in general[12,13] or participating in a disease management program.[9] However, compared to these studies the employment rate in our study population at baseline was much lower (12.4% compared to 25.6-67.1%). This is probably due to the population included in our study that is generally older and has more severe COPD.
Indeed, all patients in our study completed a PR program, reflecting that they experienced limitations in their daily life. Still, the amount of days patients were unable to perform daily activities was 2.52 times higher in patients with high breathlessness burden compared to patients with low breathlessness burden. These patients were not able to perform their daily activities, which may have a major impact on their quality of life.[29] When a patient is unable to perform household work, the informal caregiver may take over such activities. This is illustrated by

the significant higher number of days informal caregivers of patients with high breathlessness burden were unable to perform daily activities, especially in the second year. This emphasizes the additional burden on informal caregivers accompanied with increased breathlessness burden.

This study has several strengths and limitations. *First*, this is the first study of prospective patient-reported data in COPD with a follow-up of two years and a short recall period of three months. *Second*, patients with optimal pharmacological and non-pharmacological treatment have been included, since all patients completed a PR program. *Third*, several sensitivity analyses were performed, confirming that the base-case results were robust.

Some limitations of the study have to be considered. *First*, the stratification of breathlessness burden was based on the mMRC grade at baseline, while mMRC grade was assessed during each follow-up visit. Patients showed various breathlessness burden profiles, which has been shown in Supplemental Table S1. About 35.4% of participants showed a variable mMRC grade over time. *Second*, this study fully relied on patient report and was not underpinned with patient file data, except for rehabilitation and prescribed medication. This means that study results may be influenced by recall bias. However, participants knew they had to report their healthcare utilization every three months, and several participants kept notes in these periods. *Third*, calculation of costs was based on several assumptions. When it was not clear if a contact had taken place for breathing or other health problems, the frequency was equally divided over these components. Over-the-counter medication was only registered if patients mentioned it and is therefore probably not complete. The mode of transportation was not collected, and therefore transportation costs were estimated based on transportation by car. Employment status of the participants was reported at baseline of the CIROCO study and had to be extrapolated to baseline of this analysis based on data on long-term sick leave. Employment status of informal caregivers was not known at all. Therefore, valuing of impact on daily activities was done conservatively, using prices for household work. However, the sensitivity analyses showed that valuation based on the baseline employment status did not significantly affect the total societal costs. *Fourth*, the data used for this analysis were collected between 2008 and 2013. However, reference prices for 2019 were used to value healthcare costs. In the intervening years, treatment guidelines have changed.[1] *Fifth*, patients included in this study recently completed a PR program and were instructed to continue training with the physiotherapist. Also, patients have been educated in symptom recognition and therefore might contact a family doctor or medical specialist sooner. Therefore, the current results cannot be extrapolated to the general population of patients with COPD. *Finally*, the CIROCO study included some invasive tests for which patients had to come to CIRO. Therefore, it might be assumed patients for whom this was difficult (due to disease severity or due to employment) declined to participate.

Conclusions

Patients with high breathlessness burden show higher healthcare and societal costs compared to patients with low breathlessness burden, and this cost difference increases over time. Breathlessness is a complex symptom, which asks for a personalized holistic approach. Each approach of proactive palliative care that improves breathlessness burden might also influence healthcare-related costs. A recent systematic review showed the effectiveness of holistic breathlessness services on breathlessness, anxiety, depression and costs in patients with cancer.[30] These services included education, psychosocial support, self-management strategies and other appropriate interventions. Furthermore, these services include the informal caregivers and/or family and the home situation. The management of patients with high breathlessness burden should shift more to these holistic approaches in order to relieve symptoms and decrease the economic burden on society.

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Supplementary Material

Supplemental Methods 1 – Cost questionnaires

Baseline cost questionnaire

Healthcare

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1. During the past 3 months, did you **call** a family doctor? □ Yes □ No

   If yes: 1.1 What was the cause? (Please choose all that apply)

   □ Breathing problems — If yes How many times? _____
   □ Other health problems — If yes How many times? _____

---

2. During the past 3 months, did you make any healthcare visits or has any healthcare provider visited you at home? □ Yes □ No

   If yes: ***Please answer Question 3-16 else go to Question 17***

---

3. During the past 3 months, did you **visit** a family doctor? □ Yes □ No

   If yes: 3.1 What was the cause? (Please choose all that apply)

   □ Breathing problems — If yes How many times? _____
   □ Other health problems — If yes How many times? _____

---

4. During the past 3 months, did you visit a specialist? □ Yes □ No

   If yes: 4.1 What was the cause? (Please choose all that apply)

   □ Breathing problems — If yes How many times? _____
   □ Other health problems — If yes How many times? _____

---

5. During the past 3 months, did you make any other healthcare visits? □ Yes □ No

Other healthcare includes visits to the nurse, occupational therapist, physiotherapist etc (excluding physician visits).

   If yes: 5.1 What was the cause? (Please choose all that apply)

   □ Breathing problems — If yes How many times? _____
   □ Other health problems — If yes How many times? _____

---

6. During the past 3 months, did a family doctor visit you at home? □ Yes □ No

   If yes: 6.1 What was the cause? (Please choose all that apply)

   □ Breathing problems — If yes How many times? _____
   □ Other health problems — If yes How many times? _____

---

7. During the past 3 months, did other healthcare providers visit you at home? □ Yes □ No

Other healthcare includes visits to the nurse, occupational therapist, physiotherapist etc (excluding physician visits).

If yes: 7.1 What was the cause? (Please choose all that apply)

□ Breathing problems If yes How many times? _____
□ Other health problems If yes How many times? _____

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8. During the past 3 months, did you need ambulance transport? □ Yes □ No

If yes: 8.1 What was the cause? (Please choose all that apply)

□ Breathing problems If yes How many times? _____
□ Other health problems If yes How many times? _____

---

9. During the past 3 months, were you hospitalized overnight with **intensive** care? □ Yes □ No

If yes: 9.1 What was the cause? (Please choose all that apply)

□ Breathing problems If yes How many times? _____
□ Other health problems If yes How many times? _____

---

10. During the past 3 months, were you hospitalized overnight with **general** care? □ Yes □ No

If yes: 10.1 What was the cause? (Please choose all that apply)

□ Breathing problems If yes How many times? _____
□ Other health problems If yes How many times? _____

---

11. During the past 3 months, did you visit first aid/emergency care? □ Yes □ No

If yes: 11.1 What was the cause? (Please choose all that apply)

□ Breathing problems If yes How many times? _____
□ Other health problems If yes How many times? _____

---

12. During the past 3 months, have you performed a **spirometry test**? □ Yes □ No

If yes: How many times? _____

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13. During the past 3 months, have you performed an **advanced pulmonary test**? □ Yes □ No

If yes: How many times? _____

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14. During the past 3 months, have you undergone a **plain chest X-ray**? □ Yes □ No

If yes: How many times? _____

15. During the past 3 months, have you undergone a **computer tomography for chest**? □ Yes □ No

If yes: How many times? _____

16. During the past 3 months, have you been using **oxygen at home**? □ Yes □ No

If yes: How many weeks? _____

Employment

17. What is your current occupation?

□ Full-time employed	(paid employment, including self-employment)
□ Part-time employed	(less than full-time paid employment, including self-employment)
□ House-person	(subject whose main occupation is running his/her own home and family (more than 50%))
□ Retired	(retired due to age or other reason)
□ Unemployed	(currently not in paid employment)
□ Long-term sick leave	(on sick leave more than 4 weeks)

If you are part- or full-time employed:

17.1 How many hours per week do you normally work? _____ hours

If you are on long-term sick leave:

17.2 Since how many months? _____ months

17.3 What is the cause?
□ Breathing problems
□ Other health problems

18. During the past 3 months, have you been unable to perform you usual daily activities? □ Yes □ No

*(Daily activities include: **employment work** or **house-work**, not hobbies nor sports)*

If yes: 18.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many half days (≤ 4 hours)? How many full days (> 4 hours)?	_____ half days _____ full days
□ Other health problems	If yes	How many half days (≤ 4 hours)? How many full days (> 4 hours)?	_____ half days _____ full days

19. During the past 3 months, has a caregiver been unable to perform his/her usual daily activities due to your illness? □ Yes □ No

*(**Caregiver** is a person who has stayed home from work to assist you)*

If yes: 19.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many half days (≤ 4 hours)? How many full days (> 4 hours)?	_____ half days _____ full days
□ Other health problems	If yes	How many half days (≤ 4 hours)? How many full days (> 4 hours)?	_____ half days _____ full days

Follow-up cost questionnaire

Healthcare

1. During the past 3 months, did you **call** a family doctor? □ Yes □ No

If yes: 1.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

2. During the past 3 months, did you make any healthcare visits or has any healthcare provider visited you at home? □ Yes □ No

If yes: ***Please answer Question 3-16 else go to Question 17***

3. During the past 3 months, did you **visit** a family doctor? □ Yes □ No

If yes: 3.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

4. During the past 3 months, did you visit a specialist? □ Yes □ No

If yes: 4.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

5. During the past 3 months, did you make any other healthcare visits? □ Yes □ No

Other healthcare includes visits to the nurse, occupational therapist, physiotherapist etc (excluding physician visits).

If yes: 5.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

6. During the past 3 months, did a family doctor visit you at home? □ Yes □ No

If yes: 6.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

7. During the past 3 months, did other healthcare providers visit you at home? □ Yes □ No

Other healthcare includes visits to the nurse, occupational therapist, physiotherapist etc (excluding physician visits).

If yes: 7.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

8. During the past 3 months, did you need ambulance transport? □ Yes □ No

If yes: 8.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

9. During the past 3 months, were you hospitalized overnight with **intensive** care? □ Yes □ No

If yes: 9.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

10. During the past 3 months, were you hospitalized overnight with **general** care? □ Yes □ No

If yes: 10.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many times? _____
□ Other health problems	If yes	How many times? _____

11. During the past 3 months, did you visit first aid/emergency care? □ Yes □ No

If yes: 11.1 What was the cause? (Please choose all that apply)

□ Breathing problems If yes How many times? _____
□ Other health problems If yes How many times? _____

12. During the past 3 months, have you performed a **spirometry test**? □ Yes □ No

If yes: How many times? _____

13. During the past 3 months, have you performed an **advanced pulmonary test**? □ Yes □ No

If yes: How many times? _____

14. During the past 3 months, have you undergone a **plain chest X-ray**? □ Yes □ No

If yes: How many times? _____

15. During the past 3 months, have you undergone a **computer tomography for chest**? □ Yes □ No

If yes: How many times? _____

16. During the past 3 months, have you been using **oxygen at home**? □ Yes □ No

If yes: How many weeks? _____

Employment

17. During the past 3 months, have you been unable to perform you usual daily activities? □ Yes □ No

*(Daily activities include: **employment work** or **house-work**, not hobbies nor sports)*

If yes: 17.1 What was the cause? (Please choose all that apply)

□ Breathing problems If yes How many half days (≤ 4 hours)? _____ half days
How many full days (> 4 hours)? _____ full days

□ Other health problems If yes How many half days (≤ 4 hours)? _____ half days
How many full days (> 4 hours)? _____ full days

18. During the past 3 months, has a caregiver been unable to perform his/her usual daily activities due to your illness? □ Yes □ No

*(**Caregiver** is a person who has stayed home from work to assist you)*

If yes: 18.1 What was the cause? (Please choose all that apply)

□ Breathing problems	If yes	How many half days (≤ 4 hours)? How many full days (> 4 hours)?	_____ half days _____ full days
□ Other health problems	If yes	How many half days (≤ 4 hours)? How many full days (> 4 hours)?	_____ half days _____ full days

19. Are you on long-term sick leave? □ Yes □ No

If yes: 19.2 Since how many months? _____ months

19.3 What is the cause? □ Breathing problems
□ Other health problems

Supplemental Methods 2 – Assumptions

Measure	Calculations and assumptions
Number of exacerbations or hospital admissions	- If a patient answered "yes" to the question if he had contact with a healthcare professional, underwent a test or was admitted to the hospital, but for the number of days or number of times 0 was filled in, we assumed no contact had taken place; - To convert times of hospitalization to days of hospitalization, the following mean hospitalization lengths were used: - 7.6 days for general care for breathing problems;[1] - 5.2 days for general care for other health problems; [1] - 2.9 days for intensive care for breathing problems;[2] - 1.9 days for intensive care for other health problems.[2]
Cost questionnaire	- When a range is given (e.g. 2-3 liters/min), the mean value is used; - When a comment states frequency is for both lung complaints and other complaints, the frequency is divided over lung and other complaints;
Medication in general	- When information of the medicine is missing in the start visit, information was adopted from the stop visit; - When information of the medicine in start visit and stop visit didn't match, information from the stop visit was used; - If patients state to have used more than one medicine from the same medication category, only one medication was included. In case of sustained treatment, the start visit or stop visit was adjusted so medicines succeeded each other. In case of phasing out the medication, only the highest dose was included.
Medication dose	- The present information is on total daily dose. Based on FK, this dose is split up in a usual dose and number of doses per day; - In case of unknown or impossible dose, the medication name is leading and the usual dose is extracted from FK. When more doses are possible, a mean of these doses is used; - Treatment according to schedule for vitamin K antagonists was converted to: o Fenprocoumon: 2/day o Marcoumar: 1/day o Acenocoumarol: 5x1mg/day

Supplemental Methods 2. Continued

Measure	Calculations and assumptions
Medication administration route	- In case of unknown or impossible route, the usual route is extracted from FK based on medication name and dose.
Medication duration	- No duration for a course of antibiotics, corticosteroids, antivirals or other medication prescribed as a course of treatment was given within the database. Therefore, the mean value of a course of the medication was used, based on the information in the Farmacotherapeutisch Kompas (FK, www.farmacotherapeutischkompas.nl), a Dutch database of pharmacology. When a medicine is prescribed until 2 days after complaints resolved, the maximal treatment duration is used. An overview of the assumptions is stated in the appendix; - Medication data is collected each 3 months. If a patient states to have started using a medicine since the last visit, it is assumed to have started halfway the period.
Validation of medication	- The following assumptions were made about frequency of use: o Daily, at night or daily + prn: 91,25 days per 3 months; o Prn: 91,25 days per 3 months and usual daily dose; o During exercise: twice per week/26 days per 3 months; - In case of topical treatment or treatment with spray or drops, it is assumed that one tube, bottle or container is enough for one month
LTOT	- When a range is given (e.g. 2-3 liters/min), the mean value is used; - Amount of hours/day use is divided in 2 categories: o ≥15 hours/day: continuous user o <15 hours/day: non-continuous user o Use during the night, during exercise or sometimes is considered non-continuous use
Pulmonary rehabilitation program	- Costs for a rehabilitation program that took place in both year 1 and 2 was assigned to the year in which the greater part of the rehabilitation program took place

References

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2. Nationale Intensice Care Evaluatie. *Stichting NICE*, 2018. Available from: https://www.stichting-nice.nl/datainbeeld/public?subject=DURATION_OF_TREATMENT&year=2018&hospital=138&icno=0 (Accessed 29 January 2020).

Supplemental Tables

Table S1. Breathlessness burden during follow-up

		After PR program		
		Low breathlessness burden	**High breathlessness burden**	**Total**
During follow-up	Stable breathlessness burden	25 (14.0%)	61 (34.3%)	86 (48.3%)
	Decreasing breathlessness burden over time	0 (0.0%)	3 (1.7%)	3 (1.7%)
	Increasing breathlessness burden over time	6 (3.4%)	0 (0.0%)	6 (3.4%)
	Variable breathlessness burden	33 (18.5%)	30 (16.9%)	63 (35.4%)
	After baseline stable breathlessness burden[a]	18 (10.1%)	2 (1.1%)	20 (11.2%)
	Total	82 (46.1%)	96 (53.9%)	178 (100.0%)

Note: [a] These participants showed a stable breathlessness burden during the follow-up, except for the baseline visit. So participants within the group of low breathlessness burden showed low breathlessness burden at baseline, but stable high breathlessness burden during the remainder of the follow-up.
Abbreviation: PR, pulmonary rehabilitation.

Table S2. Mean costs per participant per year (in Euro's).

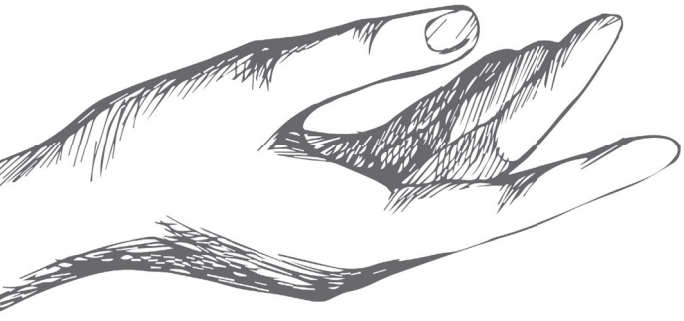
	Low breathlessness burden (n=82; 46.1%)				High breathlessness burden (n=96; 53.9%)			
	Year 1		Year 2		Year 1		Year 2	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Healthcare costs								
Outpatient	3527	3239-3810	3634	3259-4032	3792	3459-4160	4166	3665-4667
Inpatient	1606	1011-2379	1876	1159-2618	3934	2659-5569	3910	2633-5560
Diagnostics	191	145-237	274	213-344	240	192-292	311	254-372
Rehabilitation[a]	16,174[b]		17,625	6960-27,389	12,338[c]		21,109	14,184-27,471
Prescribed medication	1616	1434-1825	1772	1554-2056	1867	1641-2147	2028	1665-2493
LTOT[d]	566	416-719	713	547-873	629	509-738	681	560-782
Subtotal healthcare costs	7302	6476-8258	8830	7372-10,562	10,738	9141-12,708	14 933	12,041-18,520
Costs outside healthcare sector								
Impact daily activities participant	339	222-482	493	336-666	1153	846-1573	963	740-1196
Impact daily activities informal caregiver	49	14-95	27	5-61	23	5-53	204	66-418
Transportation	105	94-117	98	87-109	102	94-109	109	98-122
Over-the-counter medication	189	121-282	212	137-306	242	180-322	181	141-226
Subtotal costs outside healthcare sector	682	520-900	829	662-1046	1520	1210-1947	1457	1126-1821
Total societal costs	7985	7047-9087	9660	8045-11,537	12,258	10,573-14,321	16,390	13,255-19,865

Notes: Data are shown as mean (95% bootstrapped bias-corrected and accelerated confidence interval). [a] Only considering participants that underwent rehabilitation. [b] Only one participant with low breathlessness burden was admitted to pulmonary rehabilitation in year 1, so no confidence interval could be calculated. [c] Some or all bootstrap sample results are missing, so no bootstrap estimation has been performed. [d] Only considering participants that used LTOT.
Abbreviation: LTOT, long-term oxygen therapy.

Table S3. Results of sensitivity analyses on total societal costs per participant per year (in Euro's).

	Low breathlessness burden (n=82; 46.1%)				High breathlessness burden (n=96; 53.9%)			
	Year 1		Year 2		Year 1		Year 2	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Base-case								
Total societal costs	7985	7047-9087	9660	8045-11,537	12,258	10,573-14,321	16,390	13,255-19,865
Highest medication prices								
Total societal costs	9099	7945-10,567	10,709	8923-12,696	13,359	11,681-15,141	17,779	14,702-21,063
Impact on daily activities participant according to baseline employment status								
Total societal costs	8422	7378-9662	10,144	8423-12,095	12,536	10,803-14,311	16,735	13,414-20,233
Impact on daily activities informal caregiver excluded								
Total societal costs	7936	7049-8997	9632	7924-11,582	12,235	10,579-13,880	16,186	13,256-19,475
Combining all scenario's with highest costs								
Total societal costs	9536	8300-11,097	11,193	9369-13,230	13,637	11,745-15,739	18,124	15,103-21,421

Note: Data are shown as mean (95% bootstrapped bias-corrected and accelerated confidence interval).



CHAPTER 4

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

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Abstract

Dyspnea is one of the most reported symptoms of patients with advanced Chronic Obstructive Pulmonary Disease (COPD) and is often undertreated. Morphine has proven to be an effective treatment for dyspnea and is recommended in clinical practice guidelines, but questions concerning benefits and respiratory adverse effects remain. This study primarily evaluates the impact of oral sustained release morphine (morphine SR) on health-related quality of life and respiratory adverse effects in patients with COPD. Secondary objectives include the impact on exercise capacity, the relationship between description and severity of dyspnea and the presence of a clinically relevant response to morphine, and cost-effectiveness.

A single-center, randomized, double blind, placebo controlled intervention study will be performed in 124 patients with COPD who recently completed a comprehensive pulmonary rehabilitation program. Participants will receive 20-30 mg/24 h morphine SR or placebo for four weeks. After the intervention, participants will be followed for twelve weeks. Outcomes include: the COPD Assessment Test, six minute walking test, Multidimensional Dyspnea Scale and a cost diary. Furthermore, lung function and arterial blood gasses will be measured. These measures will be assessed during a baseline and outcome assessment, two home visits, two phone calls and three follow-up assessments. The intervention and control group will be compared using uni- and multivariate regression analysis and logistic regression analysis. Finally, an economic evaluation will be performed from a societal and healthcare perspective.

The current manuscript describes the rationale and methods of this study and provides an outline of the possible strengths, weaknesses and clinical consequences.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic, often progressive disease and a major cause of morbidity and mortality.[1,2] Dyspnea is one of the most frequently reported symptoms in patients with advanced COPD and many patients remain breathless despite optimal treatment of their COPD.[3,4] Previously was shown that opioids can reduce refractory dyspnea,[5-7] and therefore current (inter)national guidelines recommend opioids as palliative treatment for refractory dyspnea.[8,9] Despite these recommendations, only 2% of the outpatients with advanced COPD are using opioids.[3] Physicians mention uncertainty about benefits, fear for respiratory adverse effects and lack of evidence-based guidelines as main reasons for their reluctance to prescribe opioids.[10-12] Furthermore, a previous study suggests that one-third of patients don't show an improvement in dyspnea when treated with oral morphine for three months.[7] Currently, literature is insufficient to overcome the barriers towards opioid prescription for dyspnea.

While opioids can relieve dyspnea in patients with COPD, the effects on health-related quality of life (HRQL) and exercise capacity remain unknown. The aim of palliative care interventions is to improve HRQL,[13] but the effect of opioids on HRQL has only been assessed in three RCT's.[14-16] Consequently, a recent systematic review concerning opioid treatment for dyspnea concluded that a meta-analysis of HRQL could not be performed due to study heterogeneity and insufficient data.[17] Further, the effect of opioids on exercise capacity is unclear. In fact, two meta-analyses found no effect on exercise capacity,[5,17] mainly due to the administration of small and single doses,[18] while a recent study suggested a positive effect on exercise capacity in COPD.[19]

Another reported barrier is fear for respiratory adverse effects.[10-12] Data from patients with COPD are limited and results are conflicting. RCT's with low dose morphine showed no relevant effects on respiratory rate, blood gases or oxygen saturation. However, these studies were not designed to assess safety.[14,16,20] On the other hand, high dose oral morphine during exercise caused increased carbon dioxide levels and decreased oxygen levels in patients with COPD.[21] A recent population-based prospective cohort study showed that lower doses of opioids were not associated with increased mortality, while higher doses of opioids were associated with increased mortality, independent of partial pressure of CO_2.[22]

Furthermore, there is no consistent evidence of which patients do and don't benefit from opioid treatment.[18] Johnson et al.[23] showed that older age and more severe dyspnea predict the response to opioids. The American Thoracic Society describes three sensory descriptors of dyspnea which may be linked by specific physiological processes: sensations of work/effort, tightness and air hunger/unsatisfied inspiration.[24] To date it remains unknown whether these descriptors predict a clinical response to morphine. Finally, the cost-effectiveness of morphine treatment in patients with COPD is not yet known.

To conclude, morphine is an effective treatment for dyspnea and is recommended in current guidelines. However, questions concerning benefits and respiratory adverse effects remain. Furthermore, only two-thirds of the patients benefit from morphine treatment. Knowledge about these benefits and respiratory adverse effects is lacking and should be complemented to improve treatment for patients with COPD.

Objectives

The MORphine for DYspnea in COPD (MORDYC) study is designed to investigate the benefits and respiratory adverse effects of oral sustained release morphine (morphine SR) treatment in patients with COPD. This study primarily aims at:

1.1 studying whether and to what extent oral administration of morphine SR improves HRQL in patients with COPD;
1.2 exploring whether and to what extent oral administration of morphine SR leads to respiratory adverse effects in patients with COPD.

The secondary objectives of the study are:

2.1 to investigate the effect of oral administration of morphine SR on exercise capacity in patients with COPD;
2.2 to study the relationship between severity and description of dyspnea and the response to oral administration of morphine SR in patients with COPD;
2.3 to analyze the cost-effectiveness of oral administration of morphine SR in patients with COPD.

We hypothesize that morphine SR improves HRQL and exercise capacity, does not lead to respiratory adverse effects and is cost-effective in patients with COPD. Furthermore, we hypothesize that patients with more severe dyspnea are more likely to respond to morphine SR. Finally, we hypothesize that the description of dyspnea (work/effort, tightness and air hunger/unsatisfied inspiration) may predict the response to morphine SR.
The objective of this article is to describe the rationale and methods of the MORDYC study and to provide an outline of the possible strengths, limitations and clinical consequences.

Methods and analysis

Design
The MORDYC study is a single-center, randomized, double blind and placebo-controlled intervention study of morphine SR in outpatients with COPD, followed by a prospective cohort study in the same group of patients. A treatment period of

four weeks will be sufficient to show results of treatment with morphine SR. Since a time horizon of four weeks may be insufficient to obtain valid estimates of the cost-effectiveness of the use of morphine SR, the collection of data on costs, health status and side effects is prolonged for twelve weeks. However, from an ethical perspective, four weeks is considered to be the maximum period to withhold the placebo group from recommended treatment. Therefore, after the intervention period of four weeks, participants can decide themselves if they will be treated with morphine.

Study population

The study population will consist of adults with a confirmed diagnosis of COPD based on the Global initiative for Obstructive Lung Disease (GOLD).[1] Participants are eligible to participate when they experience severe to very severe impairment due to dyspnea (modified Medical Research Council [mMRC] Dyspnea grade 3 or 4)[25] despite optimal pharmacological and nonpharmacological treatment of their COPD.[1] According to the latest GOLD strategy, optimal pharmacological treatment for patients with high symptom burden includes treatment with a combination of a long-acting muscarinic antagonist and a long-acting β-agonist,[1] while optimal nonpharmacological treatment includes recent completion of a comprehensive pulmonary rehabilitation program.[1,26] All participants will be recruited at CIRO, a center of expertise for chronic organ failure in Horn, the Netherlands. This center offers a state-of-the-art interdisciplinary pulmonary rehabilitation program, including education, psychosocial counselling, physical exercise training, nutritional counselling, occupational therapy and exacerbation management, consistent with the latest American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation.[27] The program at CIRO is patient-tailored and lasting for 8 weeks (inpatient) or 14 weeks (outpatient).

Patients will be excluded from this study if they are aged under 18, are not able to read or fill out the questionnaires or diary, are awaiting lung transplantation, have a history of medicine misuse, use irreversible MAO blockers or opioids, have an allergy for morphine or its constituents, are pregnant or have the potential to get pregnant, have a history of convulsions or suffer from renal failure (creatinine clearance <15 ml/min), a head injury, intestinal obstruction, gastroparesis or liver disease. When a potential participant has suffered an exacerbation within two weeks before inclusion, enrolment will be postponed until two weeks after completion of the treatment for this exacerbation.

Intervention

Participants in the intervention group will receive morphine SR 10 mg capsules, administered twice daily (20 mg/24h). The control group will receive placebo capsules, which are identical in look and taste to the intervention medication. This ensures that both the participants and study staff won't be able to distinguish

the morphine and placebo capsules. Morphine and placebo will be prescribed for four weeks, while meanwhile usual clinical care is continued. The dose can be increased to three times per day 10 mg (30 mg/24h) after one or two weeks in non-responders. A non-responder is defined as a participant whose severity of dyspnea is not improved by one point on a Numeric Rating Scale (NRS) compared to baseline.[28] Dose increment will only be done if side-effects are acceptable according to the patient. To minimize side effects of morphine, all participants will receive a prescription for laxatives and anti-emetics with the instruction to use it as needed.

Study procedure

Patients will be informed about the study by the physician in CIRO during the end evaluation of their rehabilitation program. If a patient is eligible and shows interest in the study, he or she will receive the patient information letter. Participation will be verified by a phone call one week later. The baseline assessment will be scheduled a few days after this phone call. Between oral informed consent and the baseline assessment, participants will be randomized to either the intervention or the control group using a web-based random number generator. Minimization will be used to guarantee equal allocation distribution between the intervention and the control group. Randomization will be stratified for age (<55 years, 55-65 years, 65-75 years or >75 years) and impact of dyspnea (mMRC grade 3 or 4).[23] At the start of the baseline assessment, written informed consent will be obtained. At that moment, the participants will receive a jar with the intervention medication. The jars will be provided with a blinded label, ensuring that the researcher and the participant will not be able to see which intervention is allocated. After the baseline assessment, the participant's general practitioner and chest physician will be informed about study participation.

The intervention study consists of six assessments during the four weeks of intervention (Figure 1). The baseline (T0) and outcome (T5) assessments will take place in CIRO and last for 2.5 to 3 h. The investigator will visit the participants in their home environment one (T2) and two (T3) weeks after the baseline assessment, which lasts for approximately 1 h. Two days (T1) and four (T4) weeks after the baseline assessment, the investigator will call the participants. Furthermore, the participants will be asked to complete a weekly prospective cost diary during the intervention period.

At the end of the intervention study, the participants continue with the cohort study. At that moment, the participants can choose to continue morphine treatment. Since unblinding takes place when all participants have completed the intervention study, it is possible that participants from the placebo group assume they were in the intervention group and prefer to 'continue' morphine treatment. The general practitioner will be informed about this possibility and will be asked to monitor the treatment. The prospective cohort study lasts for twelve weeks after the end

of the intervention period. Participants will be followed up and will receive several questionnaires by post after four (T6), eight (T7) and twelve (T8) weeks (Table 1).

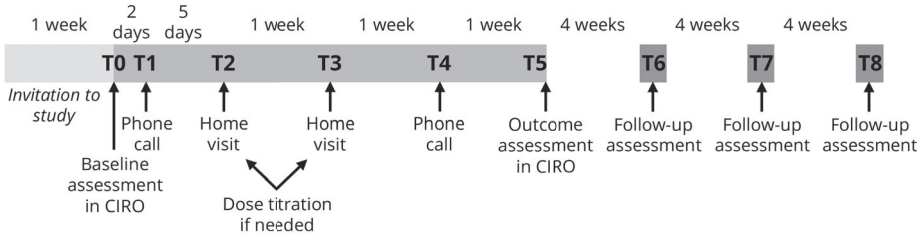

Figure 1. Study design

Outcomes

Primary outcomes

This study has two primary endpoints. HRQL will be determined using the COPD Assessment Test (CAT), which is a short and simple instrument that assesses the impact of COPD on HRQL.[29,30]

Adverse respiratory effects will be assessed by measuring partial pressure of carbon dioxide ($PaCO_2$) using arterial blood gas.

Secondary outcomes

Adverse respiratory effects will, in addition to $PaCO_2$ levels, be assessed by the following respiratory outcomes: partial pressure of oxygen (PaO_2), respiratory rate at rest, oxygen saturation (SpO_2) and transcutaneous pressure of carbon dioxide ($PtcCO_2$) using a digital monitoring system, SO_2 during the night using overnight pulse oximetry, and lung function, including forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), Tiffenau index (FEV_1/FVC) and inspiratory-to-total lung capacity ratio (IC/TLC).

Determination of functional exercise capacity consists of the following two elements. The six minute walking test (6MWT)[31] will be used to measure exercise capacity. Functional capacity will assessed by examining care dependency using the Care Dependency Scale[32] and general mobility using the Timed 'Up & Go' test.[33]

For the assessment of the relationship between severity and description of dyspnea and the response to oral morphine SR, several instruments will be used. Severity of dyspnea will be assessed using a 0-10 NRS,[34] with 0 = not breathless at all and 10 = breathlessness as bad as you can imagine. The focus period will be framed as the average dyspnea as well as the worst dyspnea during the last 24 h. At T0, the focus will also be at the average dyspnea during the last week. Description of sensory and affective dimensions of dyspnea will be verified by means of the Multidimensional Dyspnea Profile (MDP) with the last 24 h as focus period.[35,36] The mMRC scale[25] and

modified Pulmonary Functional Status and Dyspnea Questionnaire[37,38] will be used to assess impact of dyspnea.
For the economic evaluation of morphine SR, participants will complete a prospective costs diary about their healthcare use, domestic help and absence of paid or voluntary work. Generic quality of life will be determined using the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L)[39] and HRQL using the CAT. During the cohort study, the participants will be asked to fill out the CAT and EQ-5D-5L and a retrospective cost questionnaire.

Other outcomes
The following outcomes will be taken from the patient file:
- Demographic characteristics (such as date of birth, gender and marital status);
- Medical history (number of exacerbations and hospital admissions in the previous year and the Charlson Comorbidity Index[40]);
- Smoking history;
- Lung function (including FEV_1, FVC, FEV_1/FVC);
- Creatinine clearance;
- Use of medication (including use of long-term oxygen therapy and noninvasive positive pressure ventilation).

Current smoking behavior and use of medication will be verified with the participant during the baseline assessment at CIRO. Change in medication use, compliance and occurrence of exacerbations will be recorded during the remaining assessments. An exacerbation is defined as an acute event characterized by a worsening of the patient's respiratory symptoms beyond normal day-to-day variations and leading to a change in medication.[1] In addition, adverse effects will be monitored, including nausea, vomiting, drowsiness, constipation and sleeplessness (NRS; average burden in last 24 h), sleepiness (Epworth Sleepiness Scale[41]) and cognition (Montreal Cognitive Assessment[42]).
Table 1 shows the measurements performed during the intervention study and the cohort study.

Table 1. Measurements

	T0	T1	T2	T3	T4	T5	T6	T7	T8
Primary outcomes									
Health-related quality of life: COPD Assessment Test	X		X	X		X	X		X
Respiratory parameters									
Arterial blood gas, including PaO_2 and $PaCO_2$	X					X			
Respiratory rate at rest, SpO_2 and $PtcCO_2$	X		X	X		X			
Respiratory rate at rest, SpO_2 and $PtcCO_2$	X					X			
Lung function: FEV_1, FVC, FEV_1/FVC, IC/TLC	X					X			
Secondary outcomes									
Exercise capacity: six minute walking test	X					X			
Care dependency: Care Dependency Scale	X					X			
Mobility: Timed 'Up & Go' test	X		X	X		X			
Severity of dyspnea: Numeric Rating Scale	X	X	X	X	X	X	X		X
Description of dyspnea: Multidimensional Dyspnea Profile	X					X			
Impact of dyspnea: modified Medical Research Council scale	X					X	X		X
Impact of dyspnea: Modified Pulmonary Functional Status and Dyspnea Questionnaire	X					X			
Healthcare use									
Prospective cost diary		X	X	X	X	X			
Retrospective cost questionnaire							X	X	X
General quality of life: EuroQol-5 Dimensions-5 Levels	X					X	X		X
Other outcomes									
Demographics, including age, gender, marital status	X								
Medical history: Charlson Comorbidity Index	X								
COPD history: number of exacerbations and hospital admissions for COPD (< 12 months)	X								
Smoking history and behavior	X								
Current medication	X		X	X		X	X	X	X
Use of long-term oxygen or noninvasive ventilation	X					X			
Creatinine clearance	X								
Adverse effects									
Nausea, vomiting, drowsiness, constipation and sleeplessness: Numeric Rating Scale	X	X	X	X	X	X	X		X
Sleepiness: Epworth Sleepiness Scale	X					X			
Cognition: Montreal Cognitive Assessment	X					X			
Exacerbations		X	X	X	X	X	X	X	X
Compliance		X	X	X	X	X			

Abbreviations: FEV_1 = forced expiratory volume in the first second; FEV_1/FVC = Tiffenau index; FVC = forced vital capacity; IC/TLC = inspiratory-to-total lung capacity ratio; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; $PtcCO_2$ = transcutaneous pressure of carbon dioxide; SpO_2 = pulse oxygen saturation.

Sample size calculation

A total of 54 participants per treatment group are needed to detect a clinically relevant change in CAT score of 3.8 points (SD 6.1 points),[29,43] based on a significance level of 5% and a power of 90%. In addition, in order to detect a change in $PtcCO_2$ level of 1.0 kPa (SD 0.7 kPa[44]) 10 participants per treatment group are needed, based on a significance level of 5% and a power of 90%. A drop-out rate of about 13% is expected,[16] and therefore 62 participants will be included per group. Yearly, about 130 patients with COPD completing the pulmonary rehabilitation program at CIRO report an mMRC grade of 3 or 4. About 10% of these patients won't be eligible for this study because of a history of substance misuse, renal failure or because patients are already using opioids. Furthermore, based on an ongoing study among patients with advanced COPD, we expect a response rate of about 50%. Therefore, it seems reasonable to recruit 124 patients within two years.

Data management and statistical analysis

Data will be screened for missing data, which will be handled according to the guidelines of the different instruments. In order to minimize missing data, the majority of the tests and questionnaires will be performed in the presence of a researcher or research assistant. Continuous variables will be checked for normality. For all data, point measures and measures of variability will be provided. Baseline characteristics will be compared between the intervention and control group using descriptive statistics. The independent sample T-test will be used for normally distributed continuous variables, the Mann-Whitney U-test for not normally distributed continuous variables and the Chi square test for categorical variables.

Mean change in CAT-scores, respiratory parameters, 6MWT results, NRS scores for side effects, Epworth Sleepiness Scale scores and Montreal Cognitive Assessment scores will be compared between the intervention and control group using independent sample T-tests or Mann-Whitney U tests, according to the variable distribution. Subsequently, a linear mixed model will be developed to assess longitudinal changes according to trial arm. The proportion of exacerbations is compared between the intervention and control group using a Chi-squared test. Analyses will be done using an intention-to-treat approach.

To explore the relationship between the response to morphine and the severity of their dyspnea and the way participants describe their dyspnea, univariate analysis will be used, followed by binary logistic regression. Response to opioids (defined as a decrease in dyspnea NRS score by one point or more compared to baseline) will be included as dependent variable, descriptors of dyspnea (MDP) as independent variables and baseline dyspnea (NRS) as a possible confounder. Participants who discontinue morphine during the study because of lack of effect and/or intolerable adverse effects will be analyzed as non-responders.

A trial-based economic evaluation will be performed from the societal and healthcare perspective. The time horizon of the trial-based economic evaluation

will be four weeks. The intervention offered in this study is primarily expected to affect morbidity, so quality of life is considered as an important outcome in these patients. The incremental costs per Quality-Adjusted Life Year based on the EQ-5D-5L will be expressed in the incremental cost-effectiveness ratio for the societal perspective,[45] whereas additional patients with a clinically relevant improvement on the CAT will be expressed for the healthcare perspective. The cost analyses will be performed according to Dutch guidelines for cost calculations,[46] and study related costs will be excluded. Hospital resource use will be registered using the questions about exacerbations and costs outside the hospital will be registered using the cost diary and cost questionnaire. Standard sensitivity analyses and bootstrap analysis will be performed to investigate the uncertainty surrounding the incremental cost-effectiveness ratios. Based on the bootstrap results, cost-effectiveness acceptability curves will be constructed. These curves show the probability that morphine (in addition to usual clinical care) is cost-effective compared to placebo (in addition to usual clinical care) for a range of cost-effectiveness threshold values. Data collection on costs, quality of life and side effects will be prolonged for twelve weeks since a time horizon of four weeks may be insufficient to obtain valid estimates of the cost-effectiveness of morphine. Additionally, data on long-term costs and effects will be estimated using a decision analytical model with a lifelong time horizon.[47] Transition probabilities, healthcare costs, survival and health utilities will be used as input, based on the study results, literature review and, when necessary, expert opinion. The economic impact will first be estimated using fixed estimates of probabilities, costs and health outcomes. Probabilistic sensitivity analysis will additionally be performed to address uncertainty.

Ethical considerations and dissemination

The load for the participants will be minimized by visiting them at home two times and contacting them by phone two times. Furthermore, medication will be prescribed to prevent the most common adverse effects of morphine. In case of questions or concerns, participants can contact the researchers. Participants will be able to leave the study at any time for any reason without consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. During interim analysis, the proportion of hospitalized and the proportion of deceased patients will be compared between the two groups, without unblinding. The code will be broken in case of a statistically significant higher number of hospital admissions or deaths in one group, which might be related to the study medication. This study will be conducted in accordance with the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). Informed consent will be obtained from all participants before participation. Monitoring will follow the international ICH-GCP guidelines. The results will be published in appropriate well-accepted scientific journals. If desired, participants will be informed about the results at the end of the study. The protocol of the present

study is approved by the Medical Ethics Committee Maastricht UMC+ (METC152002) and is registered at ClinicalTrials.gov (NCT02429050).

Discussion

Morphine is an effective treatment for refractory dyspnea and is recommended in clinical practice guidelines.[8,9] Although effectiveness for relieve of dyspnea is proven, concerns regarding benefits and respiratory adverse effects remain. Due to this lack of knowledge, physicians are reluctant in prescribing morphine to patients with COPD. As a result, dyspnea that persists despite optimal treatment of the underlying disease is undertreated in patient with COPD. The current study is designed to provide the knowledge physicians need to optimally treat refractory dyspnea in COPD.

Strengths of this study

To date, most studies have been focusing on the effect of opioids on refractory dyspnea, with some of them collecting data on respiratory adverse effects and HRQL as secondary objective. As a consequence, the sample size calculations of these studies were only based on the change in dyspnea score and therefore not designed to assess safety of opioids. Moreover, only three RCT's on oral or parental opioids included a measure of HRQL, and their results were conflicting.[14-16] A major strength of the present study is the intended sample size, which will be based on clinical relevant changes in both the CAT score and $PtcCO_2$. This study will therefore be able to demonstrate an effect of morphine treatment, if present.

Furthermore, the present study will include measures for the intensity of dyspnea and for the description of sensory and affective dimensions of dyspnea. These outcomes will be compared between responders and non-responders. Previous studies showed conflicting results regarding characteristics of patients with COPD that will predict the response to opioids.[23,48] This knowledge is necessary to select the patients that are likely to respond to morphine without unacceptable side effects. When such a subgroup of patients can be indicated, the treatment of refractory dyspnea can be individually tailored in the future.

Other strengths are related to the study duration. Previous studies on systemic opioids were mostly of short duration, with several studies only prescribing a single dose.[20,49-51] The treatment period of four weeks in the present study will be sufficient to show beneficial effects of morphine SR treatment. In addition, this will create an opportunity to increase the dose if initially no relieve of dyspnea is achieved. Furthermore, the intervention study is followed by a cohort study of twelve weeks, making it possible to ground the model-based economic evaluation.

Finally, including participants at the end of a comprehensive rehabilitation program ensures the completion of a state-of-the-art nonpharmacological treatment.[27]

Besides that, CIRO covers the southeastern part of The Netherlands, including patients referred from both general and academic hospitals. This will improve the generalizability of the study results.

Weaknesses of this study

This study has some potential limitations. *First*, it is possible that patients are not willing to participate. In a study among Dutch chest physicians, resistance of patients is one of the mentioned reasons restraining physicians from prescribing opioids to patients with advanced COPD.[10] It is not known if this is truly the attitude of the patient or a perception of the physician. However, Abernethy et al.[14] showed that including patients with COPD in a study with morphine SR treatment is possible. *Second*, drop-out might take place because of adverse effects like nausea and constipation.[17] To minimize this risk, participants will receive a prescription for anti-emetics and laxatives. Since drop-out cannot be prevented completely, a drop-out rate of 13% is taken into account in the sample size calculation.[16] *Third*, compliance is only monitored by asking participants about their ingestion pattern and by counting the remaining capsules at the end of the intervention period. It is possible that the compliance is different and forgotten capsules are discarded. However, this is comparable to behavior of patients in daily practice. *Finally*, the sample size might be too small to have adequate power to test interaction between severity and description of dyspnea and the response to oral administration of morphine SR.

Clinical consequences

The MORDYC study will examine the benefits and possible respiratory adverse effects of oral sustained-release morphine in patients with COPD. Currently the percentage of patients receiving morphine for refractory dyspnea is very low, despite the fact that morphine is recommended in national and international guidelines. When morphine proves to have major benefits and only small adverse effects, this might abate the barriers for physicians, leading to a more effective treatment for patients with COPD with refractory dyspnea despite optimal treatment.

Furthermore, the present study will gain insight in the characteristics of patients that do and do not benefit from treatment with morphine SR. This will create the opportunity to individually tailor the treatment of these patients, with minimal adverse effects. The future focus for patients that do not respond to treatment with morphine SR or experience unacceptable adverse effect can shift to the examination of other effective treatment.

Conclusions

To conclude, treatment of refractory dyspnea is an important component of the management of COPD. Therefore, examining the benefits and respiratory adverse effects and determining the characteristics of those that will benefit from treatment is essential for the management of patients with this disease.

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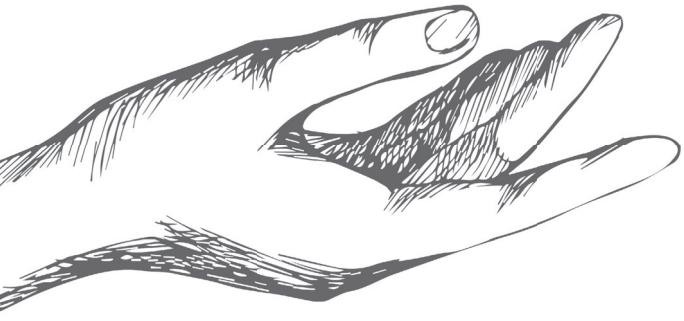

CHAPTER 5

Effect of sustained-release morphine for refractory breathlessness in COPD on health status: a randomized clinical trial

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Abstract

Importance: Morphine is used as palliative treatment of chronic breathlessness in patients with advanced chronic obstructive pulmonary disease (COPD). Evidence on respiratory adverse effects and health status is scarce and conflicting.
Objective: To assess the effects of regular, low-dose, oral sustained-release morphine on disease-specific health status (COPD Assessment Test; CAT), respiratory outcomes and breathlessness in patients with COPD.
Interventions: Participants were randomly assigned to 10 mg of regular, oral sustained-release morphine or placebo twice daily for 4 weeks, with the possibility to increase to 3 times daily after 1 or 2 weeks.
Design, setting and participants: The Morphine for Treatment of Dyspnea in Patients With COPD (MORDYC) study was a randomized, double-blind and placebo-controlled study of a 4-week intervention. Patients were enrolled between November 1, 2016 and January 24, 2019. Participants were recruited in a pulmonary rehabilitation center and 2 general hospitals after completion of a pulmonary rehabilitation program. Outpatients with COPD and moderate to very severe chronic breathlessness (modified Medical Research Council [mMRC] breathlessness grades 2-4) despite optimal pharmacological and nonpharmacological treatment were included. A total of 1380 patients were screened, 916 were ineligible and 340 declined to participate.
Main outcomes and measures: Primary outcomes were CAT score (higher scores represent worse health status) and arterial partial pressure of carbon dioxide ($PaCO_2$). Secondary outcome was breathlessness in the previous 24 hours (numeric rating scale). Data were analyzed by intention to treat. Subgroup analyses in participants with mMRC grades 3 to 4 were performed.
Results: A total of 111 of 124 included participants were analyzed (mean [SD] age, 65.4 [8.0] years; 60 men [54%]). Difference in CAT score was 2.18 points lower in the morphine group (95%CI, −4.14 to −0.22 points; p=0.03). Difference in $PaCO_2$ was 1.19 mmHg higher in the morphine group (95%CI, −2.70 to 5.07 mmHg; p=0.55). Breathlessness remained unchanged.Worst breathlessness improved in participants with mMRC grades 3 to 4 (1.33 points lower in the morphine group; 95%CI, −2.50 to −0.16 points; p=0.03). Five participants of 54 in the morphine group (9%) and 1 participant of 57 in the placebo group (2%) withdrew because of adverse effects. No morphine-related hospital admissions or deaths occurred.
Conclusions and relevance: In this randomized clinical trial, regular, low-dose, oral sustained-release morphine for 4 weeks improved disease-specific health status in patients with COPD without affecting $PaCO_2$ or causing serious adverse effects. The worst breathlessness improved in participants with mMRC grades 3 to 4. A larger

randomized clinical trial with longer follow-up in patients with mMRC grades 3 to 4 is warranted.

Introduction

Chronic breathlessness is one of the most frequently reported symptoms of patients with advanced Chronic Obstructive Pulmonary Disease (COPD).[1,2] The underlying pathophysiology is complex, and it has a considerable effect on prognosis and health status (defined as *the effect of health on the ability to perform and derive fulfillment from activities of daily life, including health-related quality of life and functional status*[3]).[4,5] Breathlessness management is an important treatment goal.[6] Previous authors proposed palliative pharmacological treatment with low-dose opioids for patients with refractory breathlessness despite optimal pharmacological and nonpharmacological treatment.[7] This recommendation has been included in international and national guidelines.[8-10] Evidence for this recommendation is still limited. Two meta-analyses reported small improvements in breathlessness after opioid treatment in patients with different life-limiting illnesses.[11,12] Analyses in patients with COPD treated for at least 4 days showed an improvement of 5 to 12 points on a 0 to 100 visual analog scale.[11,12] No effect on health status or functional performance could be shown because only a few studies included small populations. A recent study by Currow et al[13] prescribing regular, low-dose, oral sustained-release morphine for 1 week to patients with chronic breathlessness due to several conditions also showed no change in health status and suggested morphine will only reduce breathlessness in patients with severe chronic breathlessness.

Moreover, physicians remain reluctant to prescribe opioids for breathlessness in COPD for fear of respiratory depression.[14,15] A recent systematic review found no evidence for respiratory adverse effects after treatment with low-dose opioids for chronic breathlessness.[16] However, most studies were small and only a few measured arterial blood gases. To our knowledge, no large randomized clinical trials (RCTs) adequately powered to measure the effect of opioids on respiratory outcomes have yet been conducted.

Therefore, the primary aims of the Morphine for Treatment of Dyspnea in Patients With COPD (MORDYC) study[17] were to assess (1) whether and to what extent regular, low-dose, oral sustained-release morphine improves disease-specific health status in patients with moderate to very severe chronic breathlessness due to advanced COPD and (2) whether and to what extent regular, low-dose, oral sustained-release morphine leads to respiratory adverse effects. Secondary aims were to assess the effect of regular, low-dose, oral sustained-release morphine on functional performance and breathlessness.

Methods

Study design

The MORDYC study is a randomized, double blind, placebo-controlled, parallel-arm intervention study.[17] Participants were treated with regular, low-dose, oral sustained-release morphine or placebo for 4 weeks. The study protocol was approved by the medical ethics committee of Maastricht University Medical Center (METC152002). All participants provided written informed consent. Results are reported according to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

Adult patients with a confirmed diagnosis of COPD based on the Global Initiative for Obstructive Lung Disease (postbronchodilator forced expiratory volume in 1 second per forced vital capacity ratio of <0.70)[6] were recruited from CIRO (a certer of expertise for chronic organ failure in Horn, the Netherlands), Zuyderland Hospital in Heerlen, the Netherlands and VieCuri Medical Center in Venlo, the Netherlands. Inclusion criteria were modified Medical Research Council (mMRC) breathlessness grades 2, 3 or 4[18] despite optimal pharmacological and nonpharmacological treatment, including having completed a pulmonary rehabilitation program.[6] See Supplemental Methods 1 for details.

Randomization and blinding

Randomization was performed by a web-based random number generator using minimization and stratification for age (<55 years, 55-65 years, 65-75 years or >75 years) and mMRC grade.[19] Participants and investigators were blinded.

Study procedures

Participants received 10 mg of regular, oral sustained-release morphine or placebo twice daily. The dose could be adjusted to 3 times daily after 1 or 2 weeks in non-responders (<1 point improvement in severity of mean breathlessness on a 0 to 10 numeric rating scale [NRS] compared with baseline[20,21]). All participants received a prescription for macrogol (13.8 g) once daily and metoclopramide (10 mg) 3 times daily, both as needed.

After baseline, participants were contacted by phone after 2 days and 3 weeks. Home visits took place after 1 and 2 weeks (Figure 1).

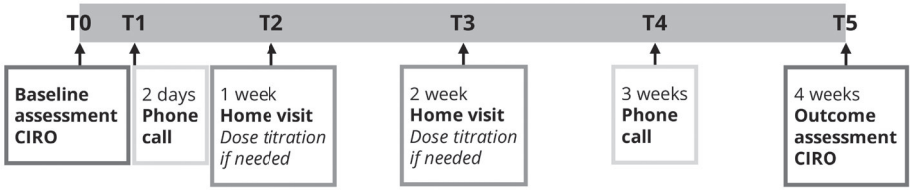

Figure 1. Study Design
Note: T indicates time.

Outcomes

At baseline, demographic and clinical characteristics were collected from the patient file or based on self-report. Disease-specific health status was determined using the COPD Assessment Test[22,23] (CAT) (higher scores represent worse health status, minimal clinical important difference [MCID] 2.0-3.0 points[24]) at time T0, T2, T3 and T5. Arterial partial pressure of carbon dioxide ($PaCO_2$) was assessed in arterial blood at T0 and T5. A priori, the project group defined a change of 7.5 mm Hg as clinically relevant.[17]

Secondary outcomes included functional performance, respiratory outcomes and severity of breathlessness. Functional performance consisted of functional exercise performance (6-minute walk test [6MWT][25]), general mobility (Timed Up and Go [TUG] test[26]) and care dependency (Care Dependency Scale [CDS][27,28]). 6MWT and CDS were assessed at T0 and T5, and the TUG test was performed at T0, T2, T3 and T5.

Secondary respiratory outcomes included (1) partial arterial pressure of oxygen (PaO_2), arterial oxygen saturation (SaO_2), percentage of time that the overnight pulse oxygen saturation (SpO_2) was below 90%, mean overnight SpO_2 and lung function at T0 and T5, and (2) respiratory rate (RR), transcutaneous carbon dioxide pressure ($PtcCO_2$) and transcutaneous SpO_2 at T0, T2, T3 and T5.

Severity of mean and worst breathlessness in the previous 24 hours was self-reported at T0 to T5 on a 0 to 10 NRS[29], with 0 being not breathless at all and 10 being the worst imaginable breathlessness.

Morphine-related adverse effects, medication use, and incidence of acute COPD exacerbations or hospitalizations were discussed during T0 to T5 (Supplemental Methods 2).

Sample size

To detect a mean (SD) change in CAT of 3.8 (6.1) points (at the time of study design the estimated MCID[22,30]), 54 participants per group were needed (significance level 5%, power 90%). Furthermore, 10 participants per group were needed to detect a mean (SD) change in $PaCO_2$ of 7.5 (5.3[31]) mm Hg. Considering a dropout rate of 13%,[32] 62 participants per group needed to be included.

Statistical analysis

Continuous data were described as mean (SD) or median (interquartile range). Categorical data were shown as number (percentage).

Given the longitudinal nature of the data, mean change between the morphine and placebo group was assessed, including time by group interaction. For $PaCO_2$, PaO_2, overnight oximetry, lung function, 6MWT and CDS a linear regression model was developed. For CAT, RR, $PtcCO_2$, SpO_2, TUG and NRS, a linear mixed-effects model was developed. Different covariance structures were considered (Supplemental Table S1) and the best-fitting model was selected using χ^2 tests. Mean difference (95% CI) between groups was presented. Post hoc subgroup analyses were performed in the original study population with mMRC grades 3 to 4 at baseline. Furthermore, post hoc analyses of the CAT on item level were performed.

Analyses were performed according to intention to treat but excluding participants who withdrew between randomization and exposure to the intervention.[33] For the analyses, SPSS version 25.0 (IBM Corp) was used. A 2-sided level of significance was set at p£0.05. Data were analyzed from September 11, 2019, to May 11, 2020.

Results

Between November 1, 2016 and January 24, 2019, 1380 patients were screened, 464 patients were eligible, and 124 participants were randomized (response rate 27%) (Figure 2). Between randomization and baseline assessment, 13 participants withdrew. The remaining 111 participants had a mean (SD) age of 65.4 (8.0) years, and 60 were men (54%) (Table 1). Participants who enrolled did not differ from those who declined to participate regarding age or sex, but participants who enrolled experienced more severe breathlessness (41 of 124 participants [33%] had mMRC grade 3 and 11 [9%] had mMRC grade 4 vs 59 of 340 nonparticipants [17%] who had mMRC grade 3 and 25 [7%] who had mMRC grade 4, p=0.009). The proportion of participants completing the treatment was 81% (n=44) in the morphine group and 89% (n=51) in the placebo group.

Health status

The difference in CAT score between the treatment groups was −2.18 points (95% CI, −4.14 to −0.22 points; p=0.03; Table 2) favoring morphine. When examining the CAT score on item level, the difference between the groups was significant for walking the stairs or hill (−0.43 points; 95% CI, −0.80 to −0.07 points; p=0.02; Table 3).

In the subgroup with mMRC grades 3 to 4, the difference between the treatment groups was not significant (−1.17 points; 95% CI, −4.17 to 1.84 points; p=0.44; Table 2), as were the scores on item level (Table 3). Results for the CAT scores per assessment are shown in Supplemental Table S2.

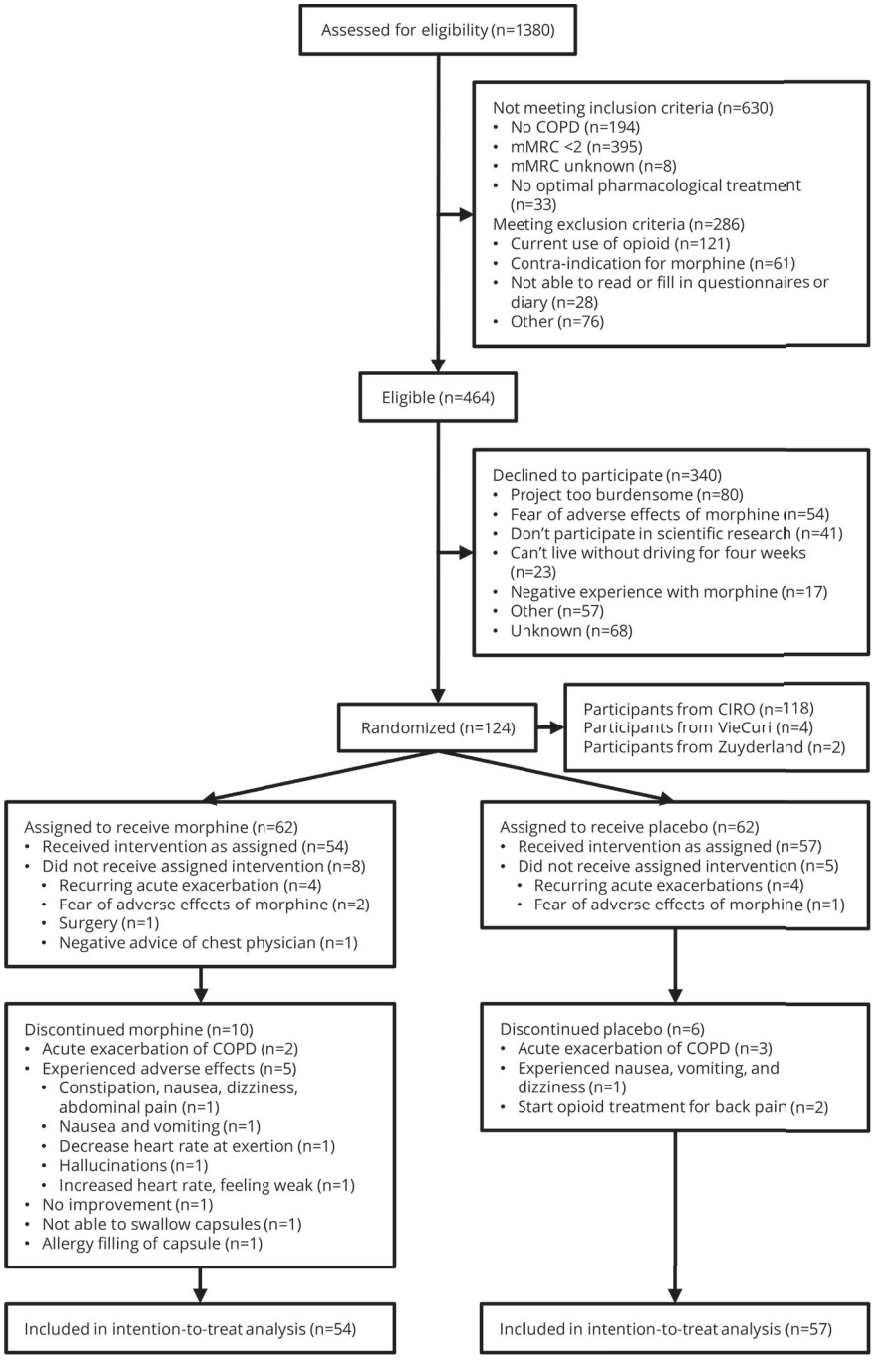

Figure 2. Flowchart of the Morphine for Treatment of Dyspnea in Patients With COPD (MORDYC) Study

Abbreviations: COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council.

Table 1. Baseline characteristics of total study population and subgroup of participants with mMRC grades 3-4

	No. (%)[a]			
	Total study population (n=111)		**Subgroup with mMRC grades 3-4 (n=49)**	
Variable	**Morphine (n=54)**	**Placebo (n=57)**	**Morphine (n=23)**	**Placebo (n=26)**
Demographics				
Age, mean (SD), y	65.0 (8.0)	65.7 (8.0)	66.6 (8.1)	64.5 (9.0)
Male	28 (52)	32 (56)	12 (52)	12 (46)
BMI, mean (SD), kg/m^2	27.6 (6.6)	27.2 (5.3)	27.5 (6.1)	26.1 (6.2)
Marital status				
Single	9 (17)	13 (23)	2 (9)	5 (19)
Married/cohabitation	42 (78)	44 (77)	19 (83)	21 (81)
In relation, but living apart	3 (6)	0 (0)	2 (9)	0 (0)
Medical characteristics				
Current smoking	7 (13)	7 (12)	3 (13)	4 (15)
Pack years, median (IQR)	40 (29.8-51.3)	40 (30-50)	40 (30-50)	40 (59-69.3)
CCI, median (IQR), points[b]	1.5 (1-2)	1 (1-3)	1 (1-2)	1 (1-3)
Prior myocardial infarction	7 (13)	4 (7)	4 (17)	1 (4)
Congestive heart failure	2 (4)	6 (11)	2 (9)	4 (15)
Peripheral vascular disease	6 (11)	6 (11)	2 (9)	1 (4)
History of cerebrovascular disease	4 (7)	4 (7)	0 (0)	3 (12)
Rheumatologic disease	1 (2)	3 (5)	0 (0)	2 (8)
Peptic ulcer disease	0 (0)	1 (2)	0 (0)	1 (4)
Mild liver disease	1 (2)	2 (2)	0 (0)	2 (4)
Diabetes mellitus	9 (17)	7 (12)	6 (26)	1 (4)
Moderate-to-severe renal disease	2 (4)	1 (2)	0 (0)	1 (4)
Diabetes mellitus with chronic complications	1 (2)	0 (0)	1 (4)	0 (0)
Cancer without metastases, leukemia or lymphoma	5 (9)	9 (16)	2 (9)	4 (15)
Exacerbations <12 months, median (IQR)	2 (1-4)	2 (0-3.5)	3 (2-4)	4 (1-4)
Hospital admissions <12 months, median (IQR)	0 (0-1)	0 (0-1)	1 (0-1)	0 (0-1)
Treatment used				
LAMA	52 (96)[c]	57 (100)	23 (100)	26 (100)
LABA	53 (98)[c]	57 (100)	23 (100)	26 (100)
ICS	43 (80)	45 (79)	18 (78)	21 (81)
LTOT	22 (41)	25 (44)	10 (43)	13 (50)
NIV	12 (22)	12 (21)	3 (13)	5 (19)

Table 1. Continued

	No. (%)[a]			
	Total study population (n=111)		Subgroup with mMRC grades 3-4 (n=49)	
Variable	Morphine (n=54)	Placebo (n=57)	Morphine (n=23)	Placebo (n=26)
Pulmonary function, median (IQR)				
FEV_1, L	0.99 (0.71-1.31)	0.95 (0.64-1.25)	0.87 (0.66-1.02)	0.88 (0.58-1.18)
FEV_1, % predicted	38 (29-53)	34 (25-49)	30 (24-42)	35 (23-51)
FVC, L	2.88 (2.39-3.74)	2.92 (2.32-3.66)	2.72 (2.03-3.66)	2.71 (2.22-3.39)
FEV_1/FVC	0.32 (0.27-0.41)	0.31 (0.25-0.42)	0.29 (0.27-0.34)	0.32 (0.26-0.44)
IC/TLC, mean (SD)	0.31 (0.09)[d]	0.31 (0.10)[e]	0.29 (0.07)[d]	0.30 (0.11)[d]
ITGV, mean (SD), L	4.79 (1.26)[d]	5.08 (1.53)[f]	5.02 (1.34)[d]	5.06 (1.85)
Clinical characteristics				
mMRC grade at T0				
2	31 (57)	31 (54)	0 (0)	0 (0)
3	20 (37)	19 (33)	20 (87)	19 (73)
4	3 (6)	7 (12)	3 (13)	7 (27)
CAT score, mean (SD)	22.8 (6.3)	21.4 (7.4)	23.2 (5.8)	24.0 (6.5)
6MWT, mean (SD), m	354 (85)[d]	343 (114)[d]	332 (84)[d]	285 (114)[d]
$PaCO_2$, median (IQR), mm Hg	40.6 (37.6-44.5)	41.4 (36.8-45.9)	42.9 (35.3-45.9)	39.9 (36.7-47.9)
SaO_2, median (IQR), %	93.1 (91.4-94.5)	93.8 (89.9-95.3)	94.2 (92.5-95.1)	93.1 (89.2-95.5)

Notes: [a] Values are written as No. (%) unless otherwise indicated. [b] None of the participants had dementia, hemiplegia, moderate or severe liver disease, metastatic solid tumor or acquired immunodeficiency syndrome. [c] One patient only used LABA therapy, and 1 patient had LAMA-LABA therapy prescribed but stopped using this on their own initiative. [d] Test not performed in 1 participant. [e] Test not performed in 3 participants. [f] Test not performed in 4 participants. **Abbreviations**: BMI, body mass index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC/TLC, inspiratory capacity to total lung capacity ratio; ICS, inhaled corticosteroids; ITGV, intrathoracic gas volume; IQR, interquartile range; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council; 6MWT, 6-minute walk test; NIV, noninvasive positive pressure ventilation; $PaCO_2$, arterial partial pressure of carbon dioxide; SaO_2, arterial oxygen saturation.

Table 2. Mean difference in outcomes for total study population and subgroup of participants with mMRC grades 3 to 4

	Morphine vs placebo			
	Total study population (n=111)		Subgroup with mMRC grades 3-4 (n=49)	
Variable	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Primary outcomes				
CAT score	−2.18 (−4.14 to −0.22)	0.03	−1.17 (−4.17 to 1.84)	0.44
$PaCO_2$, mm Hg	1.19 (−2.70 to 5.07)	0.55	1.84 (−4.95 to 8.64)	0.59
Secondary outcomes				
PaO_2, mm Hg	−3.79 (−9.70 to 2.12)	0.21	−5.92 (−15.73 to 3.90)	0.23
SaO_2, %	−1.09 (−2.93 to 0.75)	0.24	−1.72 (−5.02 to 1.58)	0.30
Respiratory rate	−1.46 (−2.84 to −0.09)	0.04	−0.73 (−2.79 to 1.34)	0.49
$PtcCO_2$, mm Hg	1.39 (−0.65 to 3.42)	0.18	1.02 (−1.78 to 3.82)	0.47
SpO_2, %	−0.33 (−0.95 to 0.29)	0.29	−0.09 (−1.09 to 0.91)	0.86
% time overnight SpO_2 below 90%	−0.04 (−19.61 to 19.52)[c]	>0.99	10.84 (−19.64 to 41.32)[a]	0.48
Overnight SpO_2, %	0.16 (−1.48 to 1.81)[c]	0.84	−0.03 (−2.90 to 2.85)[a]	0.99
FEV_1, L	−0.02 (−0.29 to 0.26)	0.91	0.04 (−0.34 to 0.42)	0.83
FEV_1, % predicted	−0.27 (−9.92 to 9.38)	0.96	2.57 (−12.07 to 17.22)	0.73
FVC, L	−0.15 (−0.68 to 0.38)	0.57	−0.17 (−0.96 to 0.63)	0.68
FEV_1/FVC	0.02 (−0.05 to 0.08)	0.60	0.04 (−0.06 to 0.14)	0.42
IC/TLC	0.02 (−0.04 to 0.07)[e]	0.58	0.03 (−0.06 to 0.11)[b]	0.56
IC, L	−0.03 (−0.49 to 0.42)[d]	0.88	−0.07 (−0.74 to 0.61)[a]	0.85
ITGV, L	−0.42 (−1.27 to 0.44)[d]	0.34	−0.65 (−2.17 to 0.88)[a]	0.40
Functional exercise performance (6MWT)	−5.07 (−61.38 to 51.20)[a]	0.86	1.49 (−87.47 to 90.46)[a]	0.97
General mobility (TUG)	−0.04 (−0.54 to 0.47)[b]	0.89	0.00 (−0.87 to 0.87)[a]	0.99
Care dependency (CDS)	−0.33 (−3.34 to 2.69)	0.83	−1.56 (−6.65 to 3.52)	0.54
Breathlessness previous 24 h (NRS)				
Mean	−0.60 (−1.55 to 0.35)	0.21	−1.31 (−2.80 to 0.17)	0.08
Worst	−0.56 (−1.41 to 0.28)	0.19	−1.33 (−2.50 to −0.16)	0.03

Notes: [a] Test not performed in 3 participants. [b] Test not performed in 1 participant. [c] Test not performed in 5 participants. [d] Test not performed in 2 participants. [e] Test not performed in 4 participants. **Abbreviations**: CAT, COPD Assessment Test; CDS, Care Dependence Scale; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; IC/TLC, inspiratory capacity to total lung capacity ratio; ITGV, intrathoracic gas volume; mMRC, modified Medical Research Council; 6MWT, 6-minute walk test; NRS, numeric rating scale; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, partial arterial pressure of oxygen; $PtcCO_2$, transcutaneous carbon dioxide pressure; SaO_2, arterial oxygen saturation; SpO_2, pulse oxygen saturation; TUG, Timed Up and Go Test.

Table 3. Mean difference in CAT item scores for total study population and subgroup of participants with mMRC grades 3 to 4

	Morphine vs placebo			
	Total study population (n=111)		Subgroup with mMRC grades 3-4 (n=49)	
Score item	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Total score	−2.18 (−4.14 to −0.22)	0.03	−1.17 (−4.17 to 1.84)	0.44
Coughing	−0.31 (−0.70 to 0.08)	0.12	−0.12 (−0.74 to 0.49)	0.70
Phlegm	−0.12 (−0.49 to 0.25)	0.52	−0.13 (−0.64 to 0.38)	0.61
Chest tightness	−0.06 (−0.55 to 0.44)	0.83	0.59 (−0.09 to 1.27)	0.09
Walking stairs or hill	−0.43 (−0.80 to −0.07)	0.02	−0.45 (−0.96 to 0.05)	0.08
Activities at home	−0.11 (−0.58 to 0.35)	0.63	−0.33 (−1.04 to 0.37)	0.35
Confidence leaving home	−0.31 (−0.86 to 0.25)	0.28	0.14 (−0.79 to 1.08)	0.76
Sleeping	−0.16 (−0.78 to 0.45)	0.60	−0.30 (−1.34 to 0.75)	0.57
Energy	−0.45 (−1.07 to 0.16)	0.15	−0.22 (−1.22 to 0.78)	0.66

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council.

Respiratory outcomes

Change in $PaCO_2$ did not differ significantly or clinically between the treatment groups (1.19 mm Hg; 95% CI, −2.70 to 5.07 mm Hg; P=0.55; Table 2). The subgroup with mMRC grades 3 to 4 also showed no significant or clinically relevant difference in $PaCO_2$ (1.84 mm Hg; 95% CI, −4.95 to 8.64 mm Hg; p=0.59; Table 2).

The difference in RR between the treatment groups was significant favoring morphine (−1.46; 95% CI, −2.84 to −0.09; p=0.04; Table 2). In the subgroup with mMRC grades 3 to 4 no difference in RR was seen (−0.73; 95% CI, −2.79 to 1.34; p=0.49; Table 2). Differences in PaO_2, SaO_2, $PtcCO_2$, SpO_2, overnight SpO_2, the amount of time SpO_2 was below 90% during the night and all lung function parameters were not significant (Table 2).

Functional performance

No difference in distance walked in the 6MWT was observed between the treatment groups in the total study population (−5.07 m; 95% CI, −61.38 to 51.20 m; p=0.86) and in the subgroup with mMRC grades 3 to 4 (1.49 m; 95% CI, −87.47 to 90.46 m; p=0.97). The TUG time and CDS scores also did not differ significantly (Table 2).

Breathlessness

There was no significant or clinically relevant change in mean or worst breathlessness in the previous 24 hours between the treatment groups (Table 2). Within the morphine group, 21 of 44 participants (48%) responded to the treatment (improvement of 1.0 point on NRS mean breathlessness); within the placebo group, 18 of 51 participants (36%) responded (p=0.25). In the subgroup with mMRC grades

3 to 4, the difference in mean breathlessness between the treatment groups was not significant (−1.31; 95% CI, −2.80 to 0.17; p=0.08; Table 2). Change in worst breathlessness in the previous 24 hours differed between the treatment groups (−1.33; 95% CI, −2.50 to −0.16; p=0.03; Table 2). Results of NRS scores for each assessment are shown in Supplemental Table S2.

Intervention and adverse effects

In 68 of 106 participants (64%) who were still in the study at time T2, treatment dose was increased to 3 times daily at T2 or T3; 27 of 51 (53%) in the morphine group and 41 of 55 (75%) in the placebo group (p=0.06). In 1 participant (2%) in the morphine group and 3 participants (5%) in the placebo group treatment dose was increased at T2 but decreased at T3 again because of adverse effects. The final mean (SD) number of capsules in the morphine group was 2.55 (0.50) capsules and in the placebo group 2.73 (0.45) capsules (P=0.07); 24 participants of 44 (55%) in the morphine group and 37 participants of 51 (73%) in the placebo group used 3 capsules/day at T5 (p=0.07; Supplemental Table S3).

Self-reported compliance was 67%, with a median number of forgotten capsules of 2 (interquartile range, 1-5). Both the proportion of noncompliant participants and the number of forgotten capsules were equal between the treatment groups (p=0.51 and p=0.44, respectively). Reasons for not taking study medication included forgetting to take the medication (n=28; 25%), feeling the medication was not helping (n=1; 1%) and experiencing adverse effects (n=6; 5%).

A total of 53 of 111 (48%) participants guessed correctly whether they received morphine or placebo (20 [37%] in the morphine group and 33 [58%] in the placebo group). A total of 20 of 111 (18%) had no idea what intervention they received (12 [22%] in the morphine group and 8 [14%] in the placebo group).

The number of participants experiencing 1 or more adverse effects of interest (nausea, vomiting and retching, drowsiness, constipation and sleeplessness) did not differ between the morphine group and placebo group (43 of 53 [81%] vs 40 of 57 [70%]; p=0.49). Change in constipation NRS scores between baseline and T5 between the treatment groups was significant (1.53 points; 95% CI, 0.44 to 2.62 points; p=0.006; Supplemental Table S4). Detailed results of participants experiencing adverse effects and change in NRS scores are shown in Supplemental Tables S4 and S5. Other spontaneously reported adverse effects did not differ between the treatment groups.

Eighteen of 111 participants (16%) experienced a moderate-to-severe COPD exacerbation (a worsening of symptoms treated with antibiotics and/or corticosteroids[6]): 7 (13%) in the morphine group and 11 (19%) in the placebo group (p=0.41). Three hospital admissions (all for COPD exacerbation) occurred, 1 of 54 (2%) in the morphine group and 2 of 57 (4%) in the placebo group (p=0.57). No morphine-related deaths occurred.

Discussion

In patients with moderate to very severe chronic breathlessness due to COPD, disease-specific health status improved after administering regular, low-dose, oral sustained-release morphine. These effects were obtained without any change in respiratory outcomes or functional performance. Regular, low-dose, oral sustained-release morphine for 4 weeks was well tolerated, with only mild opioid-related adverse effects.

To our knowledge, this is the first study powered to detect a change in respiratory outcomes of morphine treatment. Our study clearly illustrates that fear of respiratory depression or other respiratory adverse effects cannot be substantiated. Respiratory rate decreased without a change in $PaCO_2$ or PaO_2, indicating no clinically relevant differences in alveolar ventilation. Low-dose morphine treatment, therefore, seems to be safe even in this group of patients with moderate to very severe COPD. These results suggest that fear of respiratory depression, mentioned by physicians,[14,15] might be unfounded and are in accordance with our previous meta-analysis.[16]

Our results show a significant and clinically relevant improvement in CAT after morphine treatment. This improvement did not reach the predetermined MCID of the CAT as originally used for the sample size calculation.[30] However, this MCID was reassessed by Smid et al in 2017[24] and is now defined as a change of 2.0 to 3.0 points. Therefore, we conclude that the reported differences in CAT are on the lower bound of clinical relevance for this population.

Previous reviews on opioid treatment showed an effect on breathlessness, but not on health status.[11,12] Otherwise, Currow et al.[13] recently published a RCT in which 284 patients with chronic breathlessness due to several conditions were treated with regular, low-dose, oral sustained-release morphine. No effect on mean or worst breathlessness in the previous 24 hours, current breathlessness, health status or functional capacity was shown after 1 week of treatment. Where our total study population also did not show an effect on breathlessness, our subgroup with mMRC grades 3 to 4 showed an improvement on worst breathlessness of 1.33 points at 4 weeks. Moreover, the effect on mean breathlessness was 1.31 points at 4 weeks, which did not reach the level of significance, possibly due to a lack of power.

Interestingly, the morphine group reported CAT improvement on walking the stairs or hill compared with the placebo group. We cannot exclude that this improvement in daily life activities masks the expected effect on breathlessness. Indeed, palliative treatment may allow patients to be more active in daily living.[34] Patients will be able to do more before reaching the same level of breathlessness. Previous studies exploring the effect of breathlessness treatment (morphine, supplemental oxygen) on exercise capacity in laboratory settings have shown similar results.[35]

However, this suggested improvement in daily functioning was not reflected in an objectifiable change of functional performance as assessed in this study.

Morphine treatment was well tolerated by the participants of this study. The mean difference in NRS scores between the morphine and placebo group was only significant for constipation, which was consistent with other studies.[11,13] The complaints resolved after symptom treatment or early study termination. In this group of patients with COPD, there were no hospital admissions for or deaths due to morphine-related adverse effects. A large observational study on patients with COPD who are oxygen dependent also showed no association between low-dose opioids and increased hospital admissions or deaths.[36]

Strengths and limitations

Our study has several strengths and limitations. *First*, to our knowledge, this study is the first double blind, placebo-controlled, parallel-arm RCT with a 4-week morphine treatment for chronic breathlessness in patients with COPD. *Second*, to our knowledge, this is the first RCT including CAT and $PaCO_2$ as primary outcomes. Moreover, a thorough assessment of adverse respiratory effects by means of 14 outcomes was performed. *Third*, all participants completed a comprehensive pulmonary rehabilitation program ensuring treatment was both pharmacologically and nonpharmacologically optimized.

Some limitations need to be recognized. The main limitation is the large number of patients who were unwilling to participate, contributing to insufficient inclusion of our original target population. Where we expected a response rate of 50%, only 27% of eligible patients gave informed consent. As a result, we had to expand the inclusion criteria to participants with mMRC grade 2. Currow et al.[13] experienced a delayed inclusion as well, also leading to the expansion of the inclusion criteria to mMRC grade 2. As concluded by Johnson et al.,[19] patients with less severe chronic breathlessness are less likely to benefit from opioid treatment. In future studies, only patients with mMRC grades 3 to 4 should be included. *Second*, the predefined sample size was not reached for the CAT. The prior MCID of 3.8 was estimated by an anchor-based method and was the best estimate for our patient population at the time of study design.[30] The MCID was re-estimated by Smid et al.[24] by combining all known MCIDs from anchor-based and distribution-based estimations, making this MCID of 2.0 to 3.0 more accurate. Therefore, we are confident that our findings are clinically relevant. *Third*, functional performance was assessed by a standard battery of tests. At least, it can be questioned whether these forms of exercise testing are appropriate in this stage of the disease to assess daily functional performance. Direct assessment of low-grade daily life activities probably would be more appropriate.[35] Physical activity is heterogeneous, and physical activity patterns fluctuate.[37] Combining activity monitoring with, for example, Ecological Momentary Assessment can give more insight into the fluctuation of breathlessness and its effect on physical activity and quality of life over the day.[38] *Fourth*, the occurrence of adverse effects and the fact that participants were not blinded to laxative use might have compromised blinding. The occurrence of adverse effects was equal

between treatment arms, but intensity of constipation was significantly different. However, because only 48% of participants guessed their treatment (morphine or placebo) correctly, we assume blinding was only minimally compromised. In addition, although this study was one of the first with a trial duration of more than 1 week, the long-term effects of morphine and possible adverse effects remain unknown.

Conclusion

In conclusion, this study has shown that regular, low-dose, oral sustained-release morphine for 4 weeks may have a positive effect on disease-specific health status in patients with moderate to very severe breathlessness. Also, regular, low-dose, oral sustained-release morphine does not appear to lead to respiratory adverse effects. However, our results should be confirmed in a future RCT only including patients with severe to very severe chronic breathlessness and optimized pharmacological and nonpharmacological treatment of their COPD. Given the low response rate, a multicenter approach should be considered. Furthermore, to confirm and substantiate the results on CAT score, the study should include a measure of daily physical activity. Finally, to assess long-term effects and safety, more than 4 weeks of follow-up are needed.

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Supplementary Material

Supplemental Methods 1 – Participant eligibility criteria and recruitment

Inclusion criteria

- Diagnosis of COPD according to the current Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD);[1]
- Optimal pharmacological treatment, including treatment with a combination of a long-acting muscarinic antagonist (LAMA) and a long-acting β-agonist (LABA);[1]
- Grade 2, 3 or 4 dyspnea on the modified Medical Research Council (mMRC) Scale;[2]
  - o This criterion was expanded to moderate breathlessness (mMRC grade 2) to allow enrollment of predefined patient numbers.
- Optimal nonpharmacological treatment defined as completed a comprehensive pulmonary rehabilitation program.[3,4]

Exclusion criteria

- History of substance misuse;
- Exacerbation of COPD within two weeks of study enrolment;
- Waiting list for lung transplantation;
- Pregnant or childbearing potential not using contraception;
- Renal failure (creatinine clearance <15mL/min);
- Age under 18;
- Not being able to read or fill in the questionnaires or diary;
- Allergy for morphine or its excipients;
- Concomitant use of irreversible MAO blockers;
- Use of opioids;
- History of convulsions;
- Head injury;
- Intestinal obstruction;
- Gastroparesis;
- Liver disease.

Recruitment locations

Initially, participants were recruited in CIRO, Horn, The Netherlands, after completion of a PR program.[4] Due to delayed participant enrollment, participants were also recruited in Zuyderland Hospital, Heerlen and VieCuri Hospital, Venlo, The Netherlands after completion of an outpatient PR program.

Supplemental Methods 2 – Description of outcome measures

Health status

Health status was determined using the COPD Assessment Test (CAT). The CAT is a short and simple instrument that assesses the impact of COPD on health status.[5,6] The questionnaire consists of eight questions, assessing the symptoms on a scale from 0 to 5. The total score ranges from 0 to 40, with higher scores representing worse health status. The minimal clinical important difference (MCID) for the CAT is 2.0 to 3.0 points.[7] The CAT was completed on paper by the participants at T0, T2, T3 and T5.

Respiratory adverse effects

The primary respiratory outcome was arterial partial pressure of carbon dioxide ($PaCO_2$). $PaCO_2$ was assessed by arterial blood gas drawn from the radial artery at T0 and T5. Also, arterial partial pressure of oxygen (PaO_2) and arterial oxygen saturation (SaO_2) were assessed in the arterial blood. A priori, the project group defined a change of 7.5 mm Hg in $PaCO_2$ as clinically relevant.[8]

Overnight pulse oxygen saturation (SpO_2) and the time SpO_2 was below 90% during the night was assessed at T0 and T5 using a WristOx2 3150 pulse oximeter (Nonin Medical, Plymouth, USA).

Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and transcutaneous SpO_2 were assessed at T0, T2, T3, and T5 using a SenTec Digital Monitoring System (SenTec, Therwil, Switzerland) with an earlobe clip. Respiratory rate (RR) was assessed at T0, T2, T3, and T5. Finally, lung function consisted of a flow-volume measurement and a body box measurement at T0 and T5. During the flow-volume measurement, forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) were assessed, of which the Tiffenau index (FEV_1/FVC) was calculated. During the body box measurement, inspiratory capacity (IC), total lung capacity (TLC) and intra thoracic gas volume (ITGV) were assessed and afterwards the IC/TLC ratio was calculated.

Functional performance

Functional performance consisted of three tests. The 6-minute walk test (6MWT) is a valid and reliable measure to estimate functional exercise capacity in patients with chronic respiratory diseases.[9] Participants cover as many distance as possible in 6 minutes. The test was performed according to the ERS/ATS guidelines.[9] The MCID for the 6MWT is 30 m.[10] The 6MWT was performed at T0 and T5.

General mobility was examined using the Timed 'Up & Go' (TUG) test.[11] This simple test requests patients to stand up from a chair, walk 3 meters in a comfortable pace, turn, walk back and sit down on the chair again. During the test, the time is recorded. Participants performed this test twice and the best time was used for analysis.[12] The TUG test is valid and responsive in patients with COPD with a MCID of 0.9 to 1.4 sec.[13] The TUG test was performed at T0, T2, T3 and T5.

Care dependency was examined using the Care Dependency Scale (CDS).[14,15] This instrument consists of 15 items regarding basic and instrumental activities of daily living, which are each scored on a 5-point Likert Scale. Higher scores indicate less care dependency. The CDS was completed on paper by the participants at T0 and T5.

Severity of breathlessness

Severity of breathlessness was assessed using a Numeric Rating Scale (NRS) ranging from 0 to 10, with 0 being not breathless at all and 10 being the worst imaginable breathlessness.[16] The participants completed these items verbally. During all assessments, the mean and worst breathlessness in the last 24 hours was recorded. At baseline, the mean breathlessness in the last week was also determined to estimate if the day of the baseline assessment was an average day of that week. The MCID for the NRS for breathlessness is estimated at 1.0 points.[17]

Other outcomes

At baseline, the following other outcomes were recorded: demographic characteristics (age, gender, Body Mass Index and marital status), medical history (Charlson Comorbidity Index (CCI)[18] and number of exacerbations and hospital admissions in the previous 12 months[19,20]), smoking history, current smoking behavior, use of medication, use of long-term oxygen therapy (LTOT) and use of noninvasive positive pressure ventilation (NIV). At T1, T2, T3, T4 and T5, data on change in medication use, LTOT and NIV, compliance to study intervention, exacerbations and adverse effects were collected.

The CCI was completed based on the patient file and further discussed with the participant for completeness. Compliance to study intervention was recorded by asking the participant during each assessment if they missed a capsule since the prior assessment. Furthermore, if study medication was handed in at T5, the remaining capsules were counted. The occurrence of exacerbations was assessed by asking the participant if they experienced a worsening of their COPD since the prior assessment.[21] If so, the symptoms were recorded together with given medication and possible contact with a health care professional or admission to the hospital. Collection of adverse effects included nausea, vomiting and retching, drowsiness, constipation, sleeplessness, sleepiness and cognition. Nausea, vomiting and retching, drowsiness, constipation and sleeplessness were recorded during all assessments using a NRS (average burden in last 24 hours). The participants completed these items verbally.

At the end of the intervention study, the participants were asked which intervention they assumed to have received.

Supplemental Tables

Table S1. Covariance structures

	Random Intercept	Random Intercept + Random Slope	Unstructured
CAT	Chosen	Considered	Considered
Respiratory rate	Chosen	Not applicable	Considered
$PtcCO_2$	Considered	Not applicable	Chosen
SpO_2	Considered	Not applicable	Chosen
TUG	Considered	Considered	Chosen
NRS mean breathlessness	Considered	Chosen	Considered
NRS worst breathlessness	Chosen for both groups	Considered for total group Not applicable for subgroup	Considered for both groups

Abbreviations: CAT, COPD Assessment Test; NRS, Numeric Rating Scale; $PtcCO_2$, transcutaneous partial pressure of carbon dioxide; SpO_2, pulse oxygen saturation; TUG, Timed Up & Go test.

Table S2. Mean difference in CAT score and breathlessness scores per assessment for total study population and subgroup of participants with mMRC grades 3-4

	Morphine vs placebo			
	Total study population (n=111)		Subgroup with mMRC grades 3-4 (n=49)	
Variables	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
CAT				
T2	−1.45 (−3.33 to 0.44)	0.13	−0.34 (−3.16 to 2.48)	0.81
T3	−1.83 (−3.74 to 0.08)	0.06	−1.82 (−4.67 to 1.04)	0.21
T5	−2.18 (−4.14 to −0.22)	0.03	−1.17 (−4.17 to 1.84)	0.44
Mean breathlessness (NRS)				
T2	−0.11 (−0.84 to 0.62)	0.76	−0.41 (−1.46 to 0.63)	0.43
T3	−0.55 (−1.35 to 0.26)	0.18	−0.90 (−2.10 to 0.29)	0.14
T5	−0.60 (−1.55 to 0.35)	0.21	−1.31 (−2.80 to 0.17)	0.08
Worst breathlessness (NRS)				
T2	−0.02 (−0.83 to 0.80)	0.97	−0.63 (−1.73 to 0.46)	0.26
T3	−0.20 (−1.02 to 0.62)	0.63	−0.44 (−1.55 to 0.67)	0.43
T5	−0.56 (−1.41 to 0.28)	0.19	−1.33 (−2.50 to −0.16)	0.03

Abbreviations: CAT, COPD Assessment Test; NRS, Numeric Rating Scale

Table S3. Dose increase during the study

	No (%)[a]		
Variables	**Morphine (n=54)**	**Placebo (n=57)**	**p-value**
Increase T2	13 (27)	30 (55)	0.001
Increase T3	14 (29)	11 (20)	0.28
Decrease T3	1 (2)	3 (5)	0.38
Number of capsules per day after T2, mean (SD)	2.26 (0.44)	2.55 (0.50)	0.002
Number of capsules per day after T3, mean (SD)	2.53 (0.50)	2.69 (0.47)	0.10
Final number of capsules per day at T5, mean (SD)	2.55 (0.50)	2.73 (0.45)	0.07
Participants using 3 capsules per day at T5	24 (55)	37 (73)	0.07

Note: [a] Values are written as No. (%) unless otherwise indicated.

Table S4. Numeric Rating Scores for adverse effects for total study population

	Morphine vs placebo			
	Baseline to final assessment for total study population (n=111)		**Maximal difference for total study population (n=111)**	
Variables	**Mean difference (95% CI)**	**p-value**	**Mean difference (95% CI)**	**p-value**
Nausea	−0.61 (−1.57 to 0.35)	0.21	−0.61 (−1.57 to 0.35)	0.21
Vomiting and retching	−0.27 (−0.69 to 0.14)	0.20	−0.43 (−1.01 to 0.14)[a]	0.14
Drowsiness	−0.11 (−1.24 to 1.01)	0.84	1.23 (0.16 to 2.31)[b]	0.30
Constipation	1.53 (0.44 to 2.62)	0.006	1.53 (0.44 to 2.62)	0.006
Sleeplessness	−0.44 (−1,67 to 0.80)	0.48	−0.49 (−1.52 to 0.55)[b]	0.36

Notes: [a] Reached at T1. [b] Reached at T2.

Table S5. Participants experiencing worsening of adverse effects

	No (%)		
Variables	**Morphine (n=54)**	**Placebo (n=57)**	**p-value**
Nausea	16 (30)	13 (23)	0.48
Vomiting and retching	8 (15)	10 (18)	0.72
Drowsiness	27 (50)	21 (37)	0.29
Constipation	25 (46)	17 (30)	0.16
Sleeplessness	16 (30)	23 (40)	0.34

Note: A worsening was defined as ≥2 points on the NRS score.

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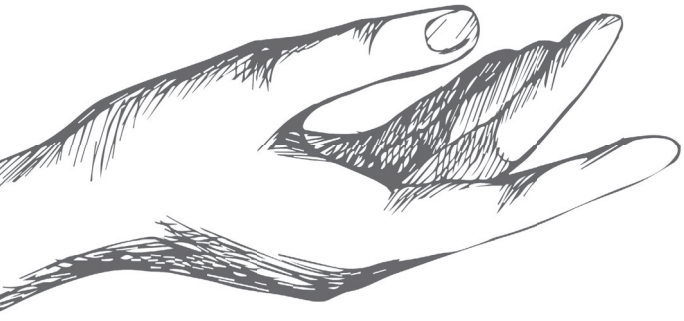

CHAPTER 6

Predictors of response to morphine for chronic breathlessness in chronic obstructive pulmonary disease: a cross-sectional study

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CHAPTER 7

Cost-effectiveness of sustained-release morphine for refractory breathlessness in COPD: a randomized clinical trial

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Abstract

Background: Chronic breathlessness is a frequent symptom in advanced chronic obstructive pulmonary disease (COPD) and has major impact on quality of life, daily activities and healthcare utilization. Morphine is used as palliative treatment of chronic breathlessness. The aim is to analyze cost-effectiveness of regular, low-dose morphine in patients with advanced COPD from a healthcare and societal perspective.

Methods: In a randomized controlled trial, participants with advanced COPD were assigned to 10 mg regular, oral sustained-release morphine or placebo twice daily for four weeks. Quality of life (COPD Assessment Test; CAT), quality-adjusted life years (QALY's; EQ-5D-5L), healthcare costs, productivity and patient and family costs were collected. Incremental cost-effectivity ratios (ICERs) using healthcare costs and CAT scores and incremental cost-utility ratios (ICURs) using societal costs and QALY's were calculated.

Results: Data of 106 of 124 participants were analyzed, of which 50 were in the morphine group (mean [SD] age 65.4 [8.0] years, 58 [55%] male). Both the ICER and ICUR indicated dominance for morphine treatment. Sensitivity analyses substantiated these results. From a healthcare perspective, the probability that morphine is cost-effective at a willingness to pay €8000 for a minimal clinically important difference of 2.0 points increase in CAT score is 63%. From a societal perspective, the probability that morphine is cost-effective at a willingness to pay €20,000 per QALY is 78%.

Conclusion: Morphine for four weeks is cost-effective regarding the healthcare and the societal perspective. To estimate the long-term costs and effects of morphine treatment, a study of longer follow-up should be performed.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by symptoms like breathlessness, fatigue and cough.[1,2] COPD is often presented with comorbidities and has a major impact on morbidity and mortality.[2] Worldwide, COPD was the ninth and sixth leading cause of loss of disability-adjusted life years in men and women, respectively, in 2017.[3]

Chronic breathlessness – breathlessness that persists despite optimal treatment of the underlying disease[4] – is one of the most frequently reported symptoms in COPD. Chronic breathlessness has a major impact on quality of life and daily life activities like work or household activities.[4-7] As chronic breathlessness worsens over time with progression of the COPD,[1,4,8] patients need increasing help from healthcare professionals and informal caregivers. Several longitudinal and cross-sectional studies in patients with COPD have shown that with increasing breathlessness disability or disease severity, both healthcare and societal costs increase.[9-13] These increased costs were mainly driven by exacerbations, hospital admissions, comorbidities and loss of productivity.[9-11,13,14] Therefore, treatment of chronic breathlessness is important in the management of COPD.[2]

Opioids have proven to be an effective palliative treatment of chronic breathlessness in patients with COPD.[15-17] However, the effect of opioids on health-related quality of life is conflicting. Two reviews reported an unclear effect of opioids on quality of life,[16,17] with three included studies reporting no effect on quality of life,[18-20] one study reporting a beneficial effect[21] and one study reporting a negative effect.[22] Meta-analyses could not be performed due to study heterogeneity and insufficient data. Subsequently, a large randomized controlled trial on the effect of morphine for breathlessness showed no effect.[23] Study populations were mixed, with the majority of patients being patients with COPD. Three studies had a duration of four to five days,[18-21] one study had a duration of one week,[23] one study a duration of two weeks[19] and one study a duration of six weeks.[22]

Although the effectiveness of morphine is known and treatment is included in national and international guidelines,[24-26] information on cost-effectiveness of morphine treatment for breathlessness is absent. Therefore, the aim of this study was to analyze the cost-effectiveness of regular, low-dose oral sustained-release morphine in patients with advanced COPD from a healthcare and societal perspective.

Material and methods

Design

The current analysis is part of the Morphine for Treatment of Dyspnea in patients with COPD (MORDYC) study. The MORDYC study is a randomized, double blind, placebo-controlled, parallel-arm intervention study.[27,28] For this analysis, only relevant aspects will be described briefly. The study was approved by the Medical Ethics Committee Maastricht UMC+ (METC152002) and registered on ClinicalTrials.gov (NCT02429050). All subjects gave their written informed consent before study start.

Participants

The study population consisted of adults with a confirmed diagnosis of COPD based on the Global initiative for Obstructive Lung Disease (GOLD).[2] Participants were eligible when experiencing moderate to very severe impairment due to breathlessness (modified Medical Research Council (mMRC) breathlessness grade 2, 3 or 4[29]) despite optimal pharmacological and non-pharmacological treatment of their COPD, including completion of a comprehensive pulmonary rehabilitation program. In addition to the exclusion criteria of the MORDYC study, which are described in detail elsewhere,[27] patients that did not complete the cost diary were excluded from this analysis.

Intervention

Participants in the intervention group received 10 mg regular, oral sustained-release morphine capsules twice daily for four weeks (20 mg/24 h), while the control group received placebo capsules with identical look and taste twice daily for four weeks. The dose was increased to three times daily (30 mg/24 h) after one or two weeks in non-responders (defined as <1 point improvement in severity of mean breathlessness on a 0 to 10 numeric rating scale [NRS] compared to baseline[30,31]). To minimize adverse effects of morphine, all participants received a prescription for laxatives and anti-emetics with the instruction to use it as needed.

Study procedures

Patients were informed about the study by the physician after completion of a pulmonary rehabilitation program. Between oral informed consent and baseline, participants were randomized to either the intervention or the control group using a web-based random number generator. Randomization was stratified for age (<55 years, 55–65 years, 65–75 years or >75 years) and impairment due to breathlessness (mMRC grade 2, 3 or 4[29]).

After baseline, the participants were visited twice in their home. Furthermore, the participants were asked to complete a weekly prospective cost diary (Figure 1).

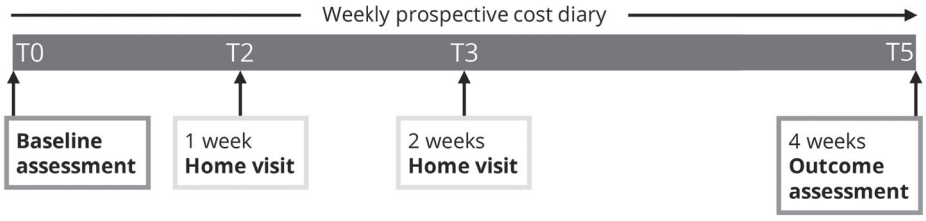

Figure 1. Study design of the MORDYC study

Measures

At baseline, information on demographics and clinical characteristics was collected from the patient file or based on self-report. This included: age, gender, body mass index (BMI), marital status, smoking behavior, comorbidities using the Charlson Comorbidity Index (CCI),[32] exacerbations and hospital admissions in the previous 12 months, lung function and functional exercise performance using the 6 minute walk distance (6MWD).[33]

Disease-specific health-related quality of life was assessed using the COPD Assessment Test (CAT).[34,35] The CAT is an eight-question instrument that assesses the impact of COPD on health-related quality of life. The impact is scored on a 0 to 5 differential scale, with higher scores indicating worse health-related quality of life. The CAT was completed at T0, T2, T3 and T5.

Generic health-related quality of life was assessed using the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L).[36,37] The EQ-5D-5L is a preference-based measure, including five domains of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is scored on five levels. Using a crosswalk set, a utility score was generated applying to the Dutch population.[38,39] The EQ-5D-5L also contains a visual analog scale (VAS) scoring the current health from 0 (*worst imaginable health*) to 100 (*best imaginable health*). The EQ-5D-5L was completed at T0 and T5.

During the four weeks of study, participants completed a comprehensive prospective cost diary at home covering employment status at baseline, healthcare utilization, medication use, household aid, absenteeism and inability to perform daily activities. All questions applied to resource use due to the COPD.

Resource use and costing

This economic evaluation was performed according to the cost manual of the Dutch National Healthcare Institute.[40] A cost-effectiveness analysis from the healthcare perspective and a cost-utility analysis from the societal perspective were performed. The following costs related to COPD and morphine treatment were included: intervention costs, other healthcare costs, costs for patient and family and productivity costs.

The resource use as registered by the participants was valued using reference prices obtained from the Dutch cost manual.[40] For resource use not covered by the Dutch

cost manual, the rate list first-line diagnostics[41] and the rate list general practitioner and multidisciplinary care[42] of the Dutch Healthcare Authority were used. Costs of medication were determined using the medication database by the Dutch National Healthcare Institute.[43] Delivery costs by the pharmacist were accounted for for medication within the drug reimbursement system. For the base case analysis, the lowest medication price was used.[40] A sensitivity analysis was performed using the highest medication prices. Costs for long-term oxygen therapy (LTOT) and non-invasive ventilation (NIV) were derived from the medication and medical device database of the Dutch National Healthcare Institute[44] and from Westfalen Medical (Deventer, the Netherlands).
Costs were calculated by multiplying the volume of resource use by the related cost price. Relevant costs prices are shown in Supplemental Table S1. All costs were indexed to 2019. Since the study duration was four weeks, no discounting was performed.

Healthcare costs
Healthcare utilization included intervention costs, contact with a general practitioner, medical specialist, nurse specialists or other healthcare professionals, use of prescribed medication, use of LTOT or NIV, hospitalization and use of professional home care.
Intervention costs included the use of morphine in the intervention group and the use of laxatives and anti-emetics in both groups. For this purpose, the number of study medication capsules, laxatives and anti-emetics used was gathered throughout the study. Since normally morphine is prescribed and followed-up by the general practitioner, a sensitivity analysis was performed including two extra consults by the general practitioner for the intervention group (one visit to the general practitioner for prescription and one telephone consult for follow-up).
Data on contact with healthcare professionals and use of professional home care were collected in the cost diary. Use of LTOT and NIV were discussed at T0 and T5. Medication use was discussed during each assessment. Information on a hospitalization was collected when applicable. When a participant was admitted to the hospital, participation in the study was terminated. However, the participant was followed-up until the event had resolved using telephone calls. For hospital admissions, only the costs for the days that would have been within the four weeks of study were included in the base case analysis. A sensitivity analysis including the costs for the complete event was performed.

Patient/family costs
Patient and family costs included medication costs not covered by the health insurance, over the counter medication, informal care, paid household aid and transportation. Costs for over the counter medication and paid household aid was registered directly in the cost diary. Transportation was calculated by using a mean

distance to the healthcare professional or hospital from the Dutch cost manual,[40] multiplied by costs for transportation based on the mode of transportation registered by the participant.

Productivity costs

Costs for productivity losses included absenteeism from paid work and absenteeism from voluntary work. Absenteeism from paid work was valued using the friction cost method, as recommended in the Dutch cost manual.[40] The friction cost method assumes that all absent or long-term sick employees are replaced after a certain friction period. This period is based on the mean time an employer needs to replace a sick or absent employee. In 2019 in the Netherlands, a period of 85 days was recommended. After this period, no costs for absenteeism are generated anymore. Absence of voluntary work (i.e. volunteering in a care home, a school or a community club) was valued according to the costs for informal care.

Analysis

Continuous data were presented as mean (SD) or median (interquartile range). Categorical data were presented as number (percentage). Cost data were presented as mean (bootstrapped BCa 95% confidence interval). Missing data on effects and resource use were imputed using single imputation, as only 4.5% of data was missing. Imputation of diary data was based on baseline clinical characteristics and the first week of diary data. Medication data in patients that dropped out during the four weeks of intervention were imputed by continuing counting until 28 days. CAT scores were analyzed using a linear mixed effects model, including time by group interaction and considering a random intercept. EQ-5D-5L utility scores and VAS scores were analyzed using a linear regression model, including time by group interaction. Quality-adjusted life years (QALYs) were assessed based on EQ-5D-5L utility scores by calculating the area under the curve.[45]

Incremental cost-effectiveness ratios (ICERs) and incremental cost-utility ratios (ICURs) were calculated using the formula $(C_m - C_p) / (E_m - E_p)$. *C* represents the average costs per participant for the four-week period and *E* represents the effect on health-related quality of life in these four weeks for the morphine group (C_m and E_m) and the placebo group (C_p and E_p). For the ICER, healthcare costs (healthcare perspective) and results of the CAT were included. In the base case analysis of the ICER, the T5 scores of the CAT were included. A sensitivity analysis using the difference between T0 and T5 for the CAT scores was conducted. For the ICUR, all costs (societal perspective) and QALYs were included.

To quantify the uncertainty around the ICER and ICUR, nonparametric bootstrapping was performed calculating 1000 simulated ICERs and ICURs. Results were plotted in cost-effectiveness planes. These planes give a visual representation of the probability that morphine is cost-effective compared to placebo by showing the distribution of simulated ICERs and ICURs in four quadrants: 1) more costly and less

effective (northwest [NW] quadrant); 2) more costly and more effective (northeast [NE] quadrant); 3) less costly and less effective (southwest [SW] quadrant); and 4) less costly and more effective (southeast [SE] quadrant).[45] An ICER or ICUR in the SE or NW quadrant shows respectively a dominant or a dominated (i.e. inferior) intervention. An ICER or ICUR in the SW or NE quadrant shows an intervention that is only favorable when the ICER or ICUR is respectively below a maximum willingness to pay (WTP) for gain in effect or beyond a minimum willingness to accept (WTA) for a loss in effect. Cost-effectiveness acceptability curves (CEAC) were created for both a minimal clinically important difference of 2.0 points improvement in CAT and for a QALY gain. These curves show the probability that the intervention is favorable for different hypothetical WTPs. In the Netherlands, the Council for Public Health and Health Care has proposed a WTP €20,000 to €80,000 per QALY, depending on the burden of disease.[46] No maximum WTP for an improvement in CAT is available. Analyses were performed according to intention-to-treat, but excluding participants that withdrew between randomization and exposure to the intervention[47] and excluding participants that generated no cost data. For the analyses, SPSS version 25.0 (IBM Corp, Armonk, NY) and Excel 2016 (Microsoft, Redmond, WA) were used.

Results

Participants

Between November 1st 2016 and January 24th 2019, 1380 patients with COPD were assessed for eligibility, 464 patients were eligible and 124 patients were randomized (Figure 2). Between randomization and baseline assessment, 13 patients withdrew participation, eight in the morphine group and five in the placebo group. Furthermore, no cost data were available for five participants, four in the morphine group and one in the placebo group. Therefore, data of 106 participants were included in the current analysis, 50 in the morphine group and 56 in the placebo group (Figure 2).

Baseline characteristics are shown in Table 1. No baseline differences were observed in the demographic or clinical characteristics. Employment status was different at baseline. In the morphine group, seven participants were employed, of whom three were on long-term sick leave. In the placebo group, three participants were employed, who were all on long-term sick leave. All participants that were on long-term sick leave were sick longer than the friction periods of 85 days and therefore generated no costs for absenteeism.

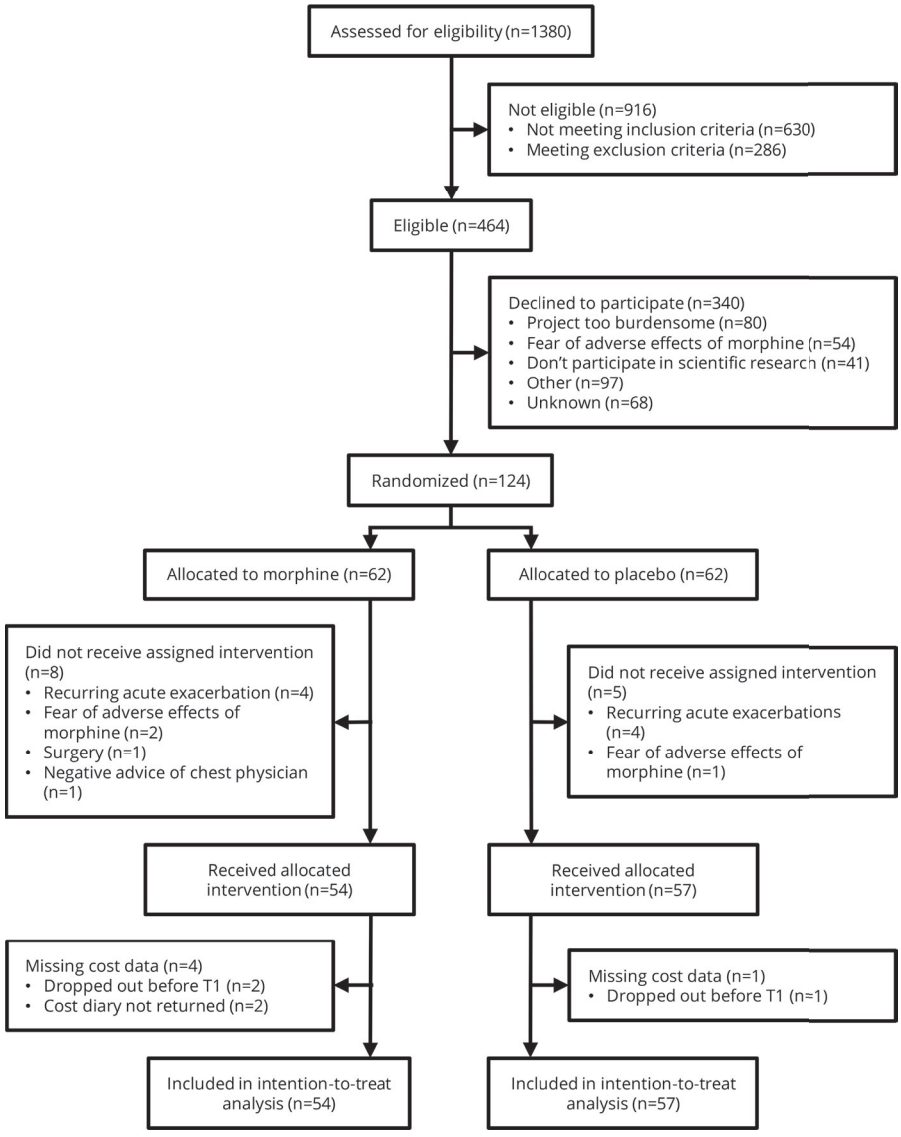

Figure 2. Flow chart

Clinical effectiveness

Table 2 shows the results of the CAT and the EQ-5D-5L. On the CAT, the morphine group scored 22.92 (7.02) points at T0 and 19.71 (7.21) points at T5. The placebo group scored 21.50 (7.02) points at T0 and 20.47 (7.13) points at T5. The total QALYs over the time horizon of four weeks were 0.050 (0.012) for the morphine group and 0.047 (0.015) for the placebo group.

Table 1. Baseline characteristics

	Total study population (n=106)	Morphine group (n=50)	Placebo group (n=56)
Demographics			
Age, mean (SD), y	65.4 ± 8.0	65.1 ± 8.0	65.6 ± 8.0
Male, No (%)	58 (55)	27 (54)	31 (55)
BMI, mean (SD)	27.6 ± 5.9	28.2 ± 6.6	27.1 ± 5.3
Marital status, No (%)			
Single	22 (21)	9 (18)	13 (23)
Married/cohabitation	82 (77)	39 (78)	43 (77)
In relation, but living apart	2 (2)	2 (4)	0 (0)
Medical characteristics			
Current smoking, No (%)	14 (13)	7 (14)	7 (13)
Pack years, median (IQR)	40.0 (30.0-50.0)	40.0 (30.0-56.3)	40.0 (30.0-50.0)
CCI, median (IQR), points[a]	1.5 (1.0-2.0)	1.5 (1.0-2.0)	1.5 (1.0-3.0)
Exacerbations <12 months, median (IQR)	2.0 (1.0-4.0)	3.0 (1.0-4.0)	2.0 (0.0-3.8)
Hospital admissions <12 months, median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Participants using LTOT, No (%)	44 (42)	20 (40)	24 (43)
Participants using NIV, No (%)	24 (23)	12 (24)	12 (21)
Pulmonary function			
FEV_1, median (IQR), l	0.96 (0.70-1.27)	1.00 (0.72-1.31)	0.93 (0.61-1.26)
FEV_1, median (IQR), %pred	35.5 (26.8-50.8)	37.5 (28.5-53.4)	34.5 (25.0-49.5)
FEV_1/FVC, median (IQR)	0.31 (0.26-0.41)	0.32 (0.27-0.41)	0.31 (0.24-0.42)
Clinical characteristics			
mMRC grade at T0, No (%)			
2	59 (58)	29 (58)	30 (54)
3	37 (35)	18 (36)	19 (34)
4	10 (9)	3 (6)	7 (12)
6MWD, mean (SD), m	347 ± 101[a]	354 ± 85	342 ± 114[a]
Employment			
Paid work, No (%)	10 (9)	7 (14)	3 (5)
Hours employment/week, median (IQR)	34.0 (23.0-48.8)	32.0 (20.0-60.0)	36.0 (32.0-40.0)
Days/week, median (IQR)	5.0 (4.0-5.0)	5.0 (4.0-5.0)	5.0 (4.0-5.0)
Sick leave, No (%)[b]	6 (60)	3 (43)	3 (100)

Notes: p>0.05 for all comparisons between morphine and placebo group. [a] Test not performed in 1 participant. [b] % of participants with paid work. **Abbreviations:** 6MWD, 6 minute walk distance; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCI, Charlson Comorbidity Index; FEV_1, forced expiratory volume in 1 second; LTOT, long-term oxygen therapy; NIV, non-invasive positive pressure ventilation.

Cost-effectiveness

Table 3 shows the costs for both treatment groups. Total healthcare costs for four weeks were €610.82 for the morphine group and €721.27 for the placebo group. Besides the intervention costs, this difference is largely explained by the difference in hospital admission costs. Costs for patient and family were higher for the morphine group (€173.46) than for the placebo group (€147.88), which was mainly due to the difference in informal care and paid household aid. Costs for productivity losses were completely generated by absenteeism from voluntary work, as all patients with a paid job were either on long-term sick leave or were not absent from their job.
For both the healthcare perspective and the societal perspective, costs in the morphine group were lower than costs in the placebo group. Combining these costs with the effects of the CAT or the QALYs resulted in both the ICER and ICUR pointing towards dominance for treatment with morphine (Table 4).

Table 2. Results of clinical outcomes (mean [SD])

	Morphine		**Placebo**	
	T0	**T5**	**T0**	**T5**
CAT	22.92 (7.02)	19.71 (7.21)[a]	21.50 (7.02)	20.47 (7.13)[a]
EQ-5D-5L utility	0.60 (0.19)	0.68 (0.17)	0.58 (0.22)	0.61 (0.21)
Total QALY's		0.050 (0.012)		0.047 (0.015)
EQ-5D-5L VAS	61.44 (16.76)	64.07 (17.74)	59.55 (18.50)	56.06 (19.25)

Notes: [a] significant difference between the groups at 5% level. **Abbreviations:** CAT, COPD Assessment Test; EQ-5D-5L, EuroQoL-5 Dimensions-5 Levels; QALY, quality-adjusted life year; VAS, visual analog scale.

The distribution of bootstrapped costs and effects for both perspectives over the four quadrants are shown in Table 4 and the cost-effectiveness planes in Figure 3a and 3c. For both perspectives, the majority of ICERs and ICURs is located in the SE quadrant indicating dominance for morphine treatment. For the bootstrapped ICERs, this was 51% and for the ICURs this was 64%.
The probability that the intervention is cost-effective given certain WTPs is shown in the CEACs in Figure 3b and 3d. At a WTP €0 for a minimal clinically important difference of 2.0 points increase in CAT score, the probability that morphine is cost-effective is 79%. This probability decreases to 68% with a WTP €1000 and eventually to 63% with a WTP €8000 or higher (Figure 3b). At a WTP €0 for one QALY gained, the probability that morphine is cost-effective is 69%. At a WTP €20,000, the probability rose to 78% and at a WTP €80,000 to 87% (Figure 3d).

Table 3. Mean costs and bootstrapped 95% CI per participant for four weeks.

	Morphine (n=50)	**Placebo** (n=56)
Healthcare costs		
Intervention costs	€10.86	€0.00
Laxatives/anti-emetics	€2.78	€2.29
General practitioner	€18.46	€27.65
Medical specialist	€37.10	€59.36
Nurse specialist	€32.96	€24.90
Other healthcare professionals	€121.76	€143.32
Hospitalization	€19.89	€115.45
Prescribed medication, covered by health insurance	€209.28	€197.12
LTOT/NIV	€38.39	€38.19
Professional home care	€109.89	€101.92
Other healthcare costs	€9.43	€11.07
Total healthcare costs	€610.82 (€489.66 - €764.11)	€721.27 (€549.60 - €936.05)
Patient and family costs		
Prescribed medication, not covered by insurance	€7.22	€9.17
Over the counter medication	€1.07	€1.25
Informal care	€95.99	€58.08
Paid household aid	€14.04	€5.89
Transportation	€9.09	€11.03
Absenteeism household work	€44.82	€52.82
Other patient and family costs	€1.21	€9.65
Total patient and family costs	€173.46 (€113.71-€235.39)	€147.88 (€89.64-€218.79)
Productivity costs		
Absenteeism paid work	€0.00	€0.00
Absenteeism voluntary work	€16.41	€2.12
Total productivity costs	16.41 (€1.34-€44.32)	€2.12 (€0.32-€4.58)
Total costs	**€800.69 (€646.68-€972.12)**	**€871.27 (€679.23-€1121.86)**

Sensitivity analyses

Table 4 shows the cost-effectiveness for the different sensitivity analyses. All of the sensitivity analyses resulted in ICERs and ICURs indicating dominance for morphine treatment.

Table 4. Costs, effects and incremental cost-effectiveness ratios (ICERs) for the base case analysis and sensitivity analyses

		Costs (€)	Effect[a]	ICER/ICUR	NE	NW (inferior)	SW	SE (dominant)
Base case analysis								
Incremental Cost-Effectiveness analysis	Placebo	721.27	20.39					
	Morphine	610.82	19.88	Dominant	11%	10%	28%	51%
Incremental Cost-Utility analysis	Placebo	871.27	0.047					
	Morphine	800.69	0.050	Dominant	25%	6%	5%	64%
Sensitivity analysis: highest medication prices								
Incremental Cost-Effectiveness analysis	Placebo	783.95	20.39					
	Morphine	679.25	19.88	Dominant	11%	9%	26%	53%
Incremental Cost-Utility analysis	Placebo	946.35	0.047					
	Morphine	879.67	0.050	Dominant	27%	7%	6%	62%
Sensitivity analysis: 2 extra consults general practitioner for prescription morphine and follow-up								
Incremental Cost-Effectiveness analysis	Placebo	721.27	20.39					
	Morphine	664.06	19.88	Dominant	19%	16%	22%	43%
Incremental Cost-Utility analysis	Placebo	871.27	0.047					
	Morphine	853.93	0.050	Dominant	42%	8%	3%	47%
Sensitivity analysis: complete hospital admission								
Incremental Cost-Effectiveness analysis	Placebo	721.27	20.39					
	Morphine	660.55	19.88	Dominant	22%	14%	21%	42%
Incremental Cost-Utility analysis	Placebo	871.27	0.047					
	Morphine	850.42	0.050	Dominant	37%	7%	4%	52%
Sensitivity analysis: effect difference scores								
Incremental Cost-Effectiveness analysis	Placebo	721.27	−1.11					
	Morphine	610.82	−2.58	Dominant	32%	3%	5%	61%

Note: [a] Higher CAT scores indicate worse quality of life. Effects on the CAT are based on T5 scores or the difference between T0 and T5. **Abbreviations:** ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; NE, north-east quadrant; NW, north-west quadrant; SE, south-east quadrant; SW, south-west quadrant.

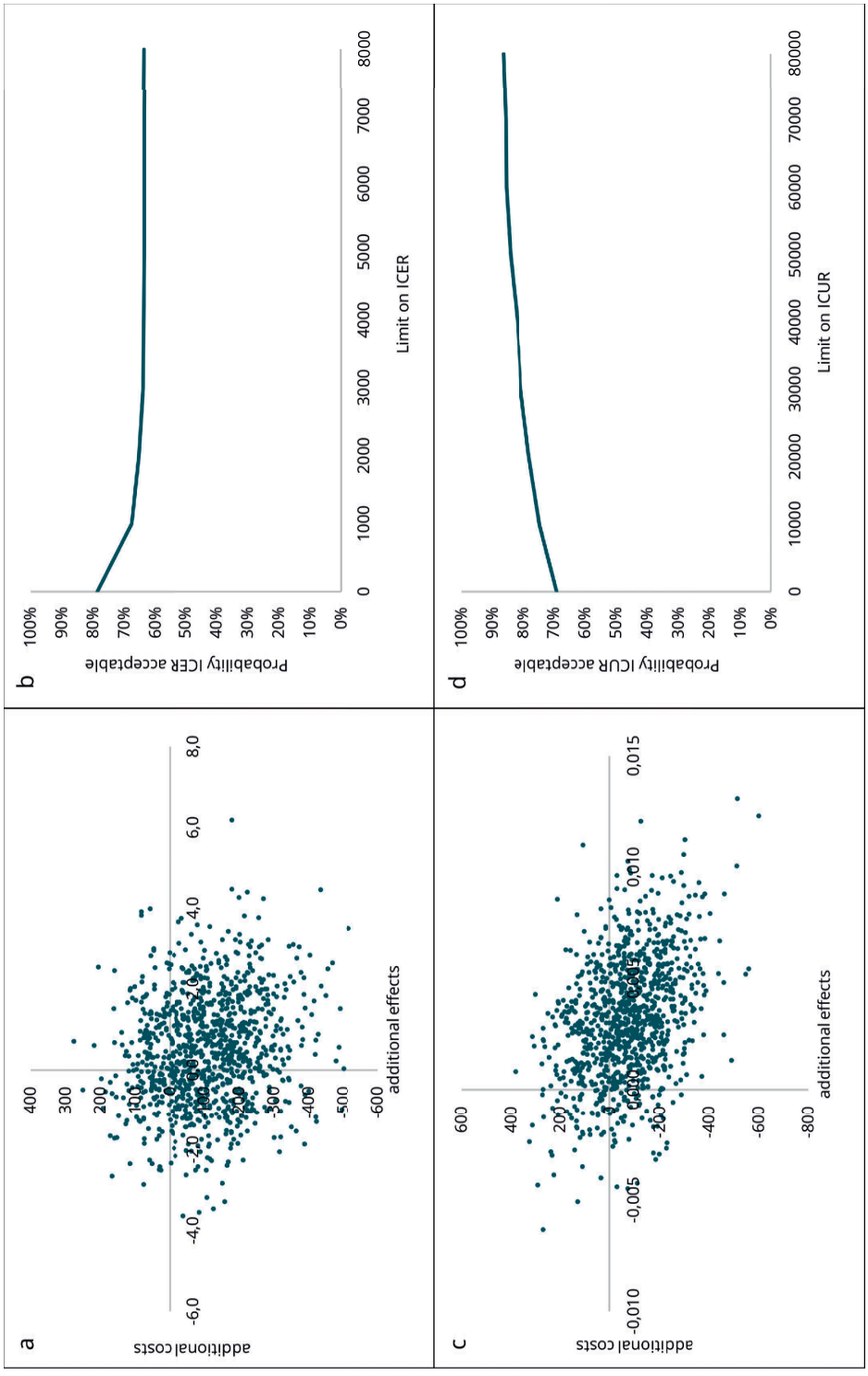

Figure 3. Cost-effectiveness planes and corresponding CEACs

Notes: Cost-effectiveness planes visualize the probability that morphine is cost-effective compared to placebo by showing the distribution of simulated ICERs and ICURs in four quadrants: 1) more costly and less effective (NW quadrant); 2) more costly and more effective (NE quadrant); 3) less costly and less effective (SW quadrant); and 4) less costly and more effective (SE quadrant). Cost-effectiveness acceptability curves show the likelihood that the intervention is favorable for different hypothetical maximum willingness to pay. (A) cost-effectiveness plane of CAT scores (healthcare costs per point CAT score increase); (B) cost-effectiveness acceptability curve of costs per 2.0 points in CAT score improved; (C) cost-effectiveness plane of QALY scores (societal costs per QALY gained); (D) cost-effectiveness acceptability curve of costs per QALY gained. **Abbreviations:** CEAC, cost-effectiveness acceptability curve; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio.

Discussion

To our knowledge, this is the first cost-effectiveness analysis of regular, low-dose, oral sustained-release morphine treatment for chronic breathlessness in patients with COPD. Our study showed that the intervention reduced healthcare and societal costs. Both from a healthcare as from a societal perspective, regular, low-dose, oral sustained-release morphine treatment was cost-effective. Sensitivity analyses showed that these results were robust.

CAT scores improved in both groups with the effect in the morphine group being larger, as was reported before by the authors.[28] This improvement was both significant and clinically relevant[48] and reported after four weeks. Previous studies that showed no effect of oral opioids on quality of life all had a duration of four days to two weeks.[18-20,23] One study showed a negative effect of oral morphine on mastery after six weeks.[22] This study included a similar patient population as the MORDYC study and disease-specific quality of life was the primary outcome. However, the number of included patients was much smaller, which could have explained the negative effect. Also, the baseline level of quality of life was unknown.

EQ-5D-5L scores showed results in the same direction as CAT scores, indicating that morphine has a positive effect on generic health-related quality of life as well after four weeks of treatment. However, this effect was rather small. It is not known if this positive effect on generic and disease-specific health-related quality of life persists for the longer term. So a study of longer duration is needed.

Both healthcare costs and societal costs were lower in the morphine group compared to the placebo group, although these differences were not significant. The largest difference in healthcare costs was shown for hospital admissions. Previous studies have shown that hospital admissions are main cost drivers for patient with COPD and high breathlessness burden.[9-13] Hospital admissions are events that generate large costs in a short period. The current study was of short duration, in which it can be expected that little hospital admissions take place. The sensitivity analysis showed that inclusion of costs for the complete hospitalization, instead of only the days that were within the study duration, had no major influence on the probability that morphine is cost-effective.

Main cost drivers in the current study were medication use and contact with healthcare professionals. Since maintenance medication generates constant costs, medication use is a known cost driver.[10-12] For a population of post-rehabilitation patients, who are advised to continue exercising under supervision of a physiotherapist, it has been shown that contact with other healthcare professionals is a cost driver.[13]

Morphine is often prescribed by the general practitioner in the Netherlands, while general practitioners have a paramount role in palliative care provision.[49] Close follow-up of morphine treatment is necessary to observe possible adverse effects in the first period of treatment and to prevent possible dependence. We considered

this follow-up was mainly performed by telephone consult. A sensitivity analysis was performed including costs for one practice visit and telephone consult, which showed this did not affect the dominance of the ICER and ICUR.
Productivity costs were singly determined by absenteeism from voluntary work. Only 9% of our population was still employed, which is common in this disabled population.[10,12,13] Those patients that were employed were either on long-term sick leave or were not absent from work. Since we used the friction cost method, no costs were calculated for patients on long-term sick leave. In many countries, the human capital method is more widely applied.[50] This method includes all costs for loss of work due to illness and related treatments. In the case of a follow-up longer than the friction period, this would lead to considerable different results.[51] However, since the MORDYC study had a follow-up period of four weeks, patients with a paid job were already absent at study inclusion and employment status did not change during the follow-up, applying the human capital method would only reflect the costs of COPD and would not be related to treatment effects.
In the Netherlands, the WTP threshold for a gain in one QALY is €20,000 to €80,000. At a WTP threshold of €20,000, the probability that morphine is cost-effective is 78%. Concerning the CAT, at a WTP €0 for a gain of the minimal clinically important difference of 2.0 points the probability that morphine is cost-effective is 79%, since this is the amount of ICERs that falls in the SE and SW quadrants (all cost saving or dominant). With increasing WTP thresholds, the probability that morphine is cost-effective gradually decreases down to 63% at a WTP threshold of €8000. This indicates that even with a low, conservative WTP morphine is cost-effective, although there is no accepted WTP threshold for a minimal clinically important difference of 2.0 points improvement in CAT score. This WTP threshold is expected to be much lower than that of the QALY, suggesting that morphine has a high probability of being cost-effective.

Strengths and limitations
This study has several strengths and limitation. *First*, to our knowledge this was the first cost-effectiveness and cost-utility analysis of oral morphine treatment for chronic breathlessness in patients with COPD. Since these analyses were part of a randomized controlled trial, participants were blinded to treatment allocation. Also, participants were optimally treated for their COPD, including having completed a comprehensive pulmonary rehabilitation program. *Second*, both the societal and the healthcare perspective are covered. Morphine is a treatment for breathlessness and therefore assumed to decrease healthcare utilization. However, due to the major impact of breathlessness on daily life activities,[4-7] covering the complete spectrum of societal costs gives a better picture of the effects of morphine treatment. Furthermore, the implementation of the societal perspective in the design of the study may be considered a strength. Since a big part of the patients with COPD are retired or unable to perform a paid job, only including work-related productivity

costs would lead to an underestimation of societal costs. Therefore, costs for inability to perform voluntary work or daily life activities were included as well. *Finally*, several sensitivity analyses were performed in order to ground the base case analysis. This included a sensitivity analysis that mimics usual care by considering costs for consults by the general practitioner for prescription and follow-up of morphine treatment.

Several limitations have to be considered. *First*, the data collection was only for four weeks. Although this is one of the first and longest randomized controlled trials of opioid treatment for chronic breathlessness in COPD, the long-term effects and costs of morphine treatment remain unknown. It has been shown that hospitalizations are one of the main cost drivers in patients with COPD and severe breathlessness.[9-13] In this short follow-up, three patients were admitted to the hospital. A recent observational study in the Netherlands showed 0.73 hospital admissions per patient per year for breathing problems in patients with COPD and high breathlessness burden (mMRC 2 to 4). Converting this to our study would have meant six hospital admissions. Therefore, healthcare costs might be underestimated. Furthermore, it is not known if the effect of morphine on health-related quality of life persists after four weeks. A study with longer follow-up should be considered to estimate the long-term costs and effects of morphine treatment in these patients. *Second*, no baseline data on healthcare utilization and activities of daily life were collected. Therefore, we cannot be certain that the difference in cost data between the morphine and placebo group was created by the morphine treatment. Especially in the case of informal care and voluntary work, which were the main differences in costs for patient and family and productivity costs. However, due to the randomization of treatment allocation, we may assume groups are equal at baseline. *Third*, results of this analysis are only applicable for patients who completed a comprehensive pulmonary rehabilitation program. However, since low-dose, oral, sustained-release morphine is indicated in chronic breathlessness despite optimal treatment of the underlying disease and pulmonary rehabilitation is indicated to optimize symptoms of COPD, results are generalizable to the patients in which low-dose morphine is indicated for chronic breathlessness. *Finally*, clinical effectiveness differed between the longitudinal regression model and the cost-effectiveness analysis. In the cost-analysis data were imputed and afterwards the mean of T5 scores was calculated, while in the regression model the data of all four assessments were taken into account. Longitudinal regression modelling showed that morphine treatment for four weeks improves health-related quality of life significant and clinically relevant.[28]

Conclusion

In conclusion, this study has shown that regular, low-dose, oral sustained-release morphine treatment for four weeks has a positive effect on disease-specific and generic health-related quality of life and healthcare and societal costs and therefore can be considered cost-effective in patients with advanced COPD and

chronic breathlessness. Given the prevalence and burden of chronic breathlessness in patients with advanced COPD, morphine treatment should be considered in this patient population when optimal pharmacological and non-pharmacological treatment does not provide adequate relief. To estimate the long-term cost-effectiveness of morphine treatment, a model-based analysis should be considered.

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Supplementary Material

Table S1. Overview of most important cost categories with unit prices.

Cost category	Unit price (2019)	Source
Intervention costs		
Morphine		
Low	€0.18	Medicijnkosten.nl[1]
High	€0.19	Medicijnkosten.nl[1]
Laxatives (Movicolon) low/high	€0.41	Medicijnkosten.nl[1]
Anti-emetics (Metoclopramide)		
Low	€0.07	Medicijnkosten.nl[1]
High	€0.08	Medicijnkosten.nl[1]
Healthcare costs		
General practitioner		
Visit GP practice	€34	Dutch cost manual[2]
Home visit	€52	Dutch cost manual[2]
Consult by phone	€18	Dutch cost manual[2]
Repeated prescription	€0	Dutch cost manual[2]
Visit GP center	€173	Rate list general practitioner and multidisciplinary care of the Dutch Healthcare Authority (Nederlandse Zorgautoriteit)[3]
Medical specialist		
Visit	€95	Dutch cost manual[2]
Consult by phone	€49	(calculated from) Dutch cost manual[2]
Nurse specialist		
Visit	€95	(calculated from) Dutch cost manual[2]
Consult by phone	€49	(calculated from) Dutch cost manual[2]
Other healthcare professionals		
Visit physiotherapist	€34	Dutch cost manual[2]
Home visit physiotherapist	€52	(calculated from) Dutch cost manual[2]
Visit dietician	€34	(calculated from) Dutch cost manual[2]
Home visit dietician	€52	(calculated from) Dutch cost manual[2]
Visit psychologist	€67	Dutch cost manual[2]
Visit speech therapist	€31	Dutch cost manual[2]
Visit nurse practitioner	€34	(calculated from) Dutch cost manual[2]
Hospitalization (day)	€497	Dutch cost manual[2]
Prescribed medication, covered by insurance	Variable	Medicijnkosten.nl[1]
LTOT (day)	€2,96	Westfalen Medical (Deventer, the Netherlands)
NIV (day)	€0.97	Medication and medical device database of the Dutch National Healthcare Institute (Zorginstituut Nederland)[4]

Table S1. Continued

Cost category	Unit price (2019)	Source
Professional home care		
Nursing and caring (hour)	€21	Dutch cost manual[2]
Household activities (hour)	€52	Dutch cost manual[2]
Other healthcare costs	Variable	Reported by participants in cost diary
Patient and family costs		
Prescribed medication, not covered by insurance	Variable	Medicijnkosten.nl[1]
Over the counter medication	Variable	Reported by participants in cost diary
Informal care (hour)	€14.63	Dutch cost manual[2]
Paid household aid	Variable	Reported by participants in cost diary
Transportation		
By car or public transportation	€0.20	Dutch cost manual[2]
Parking costs hospital	€3.13	Dutch cost manual[2]
By taxi, base rate	€3.08	Dutch cost manual[2]
By taxi, rate per km	€2.78	Dutch cost manual[2]
Absenteeism household work (hour)	€14.63	Dutch cost manual[2]
Other patient and family costs	Variable	Reported by participants in cost diary
Productivity costs		
Absenteeism paid work (hour)	€36.31	Dutch cost manual[2]
Absenteeism voluntary work (hour)	€14.63	Dutch cost manual[2]

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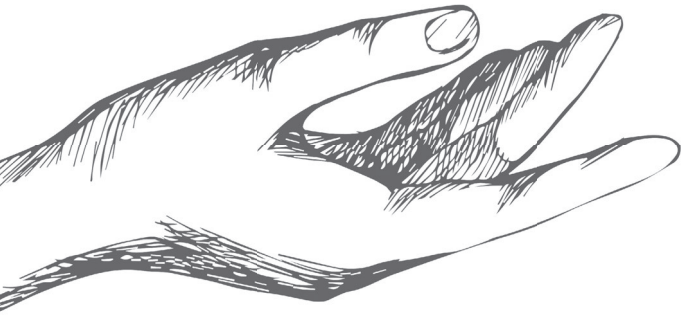

CHAPTER 8

Attitudes of patients with chronic breathlessness towards treatment with opioids

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To the editor:

Breathlessness is the most common symptom in advanced chronic lung disease or chronic heart failure (CHF).[1] Opioids are recommended for palliative treatment of breathlessness persisting despite optimal pharmacological and non-pharmacological treatment.[2,3] However, physicians don't always consider opioids for chronic breathlessness[4,5] and experience barriers when considering opioids, such as resistance of patients.[6] This can limit effective palliative treatment. Qualitative studies in patients with COPD and CHF revealed fear of dependence and fear of imminent death as the most important barriers to opioid use. The reason to start treatment was to do as much as possible.[7-9] These qualitative studies were only conducted in small patient populations. Therefore, our aims were 1) to assess the willingness of patients with chronic lung disease or CHF to use opioids for breathlessness, irrespective of a current indication for opioid treatment and 2) to assess their barriers towards opioid use and reasons to use opioids. Finally, we aimed to compare willingness differences according to sex, age, educational level, diagnosis and breathlessness severity.

An exploratory convenience sample of 175 patients referred for a baseline assessment prior to pulmonary or heart failure rehabilitation was recruited, independent of their level of breathlessness. Patients were excluded when they could not read or write, had not mastered Dutch, aged <18 years or were unable to give informed consent. The Maastricht University Medical Centre (MUMC+) medical ethical committee (Maastricht, the Netherlands), reviewed the study protocol and concluded that the study didn't fall under the Medical Research Involving Human Subjects Act (METC 2018-0790). Patients completed a survey including: demographic characteristics, educational level, previous and current opioid use (opioid, dosage and reason for prescription) and willingness to use opioids for breathlessness. Patients willing to use opioids and patients who had experience with opioids were asked to indicate their reasons to use opioids; patients unwilling to use opioids were asked to indicate their barriers. Patients who were indecisive were asked to indicate their barriers against and the reasons to use opioids. In addition, patients were invited to report reasons other than those predefined using a free-text field. The predefined reasons were selected based on previous research,[7-9] expert opinion of the project group and experience from patient inclusion for an opioid trial (MORDYC).[10] Disease characteristics (diagnosis, disease history, lung function, 6-min walk distance [6MWD][11]) and breathlessness severity (modified Medical Research Council [mMRC] scale)[12] were recorded using chart review.

Table 1. Attitudes of patients with chronic breathlessness to opioid treatment

	Willing to use opioids			Not willing to use opioids			Indecisive		
	Total	Used opioid before	Never used opioid	Total	Used opioid before	Never used opioid	Total	Used opioid before	Never used opioid
Subjects	64	25[a]	36[a]	44	24[a]	18[a]	67	23[a]	43[a]
Reasons to use opioids									
If recommended by physician	40 (63)	18 (72)	20 (56)		NA		49 (73)	16 (70)	33 (77)
Doing as much as possible to feel better	47 (73)	18 (72)	27 (75)				29 (43)	11 (48)	18 (42)
If it doesn't help, it doesn't harm	18 (28)	8 (32)	8 (22)				7 (10)	2 (9)	5 (12)
Heard of positive effects	6 (9)	2 (8)	4 (11)				7 (10)	1 (4)	5 (12)
Read about positive effects	5 (8)	2 (8)	2 (6)				4 (6)	3 (13)	1 (2)
If recommended by other healthcare professional	6 (9)	0 (0)	6 (17)				1 (1)	1 (4)	0 (0)
Good experiences of loved one(s)	1 (2)	0 (0)	1 (3)				2 (3)	0 (0)	2 (5)
Other	0 (0)	0 (0)	0 (0)				1 (1)	0 (0)	1 (2)
Reasons not to use opioids									
Concerns about adverse effects		NA		28 (64)	15 (63)	11 (61)	21 (31)	10 (43)	11 (26)
Fear of adverse effects				17 (39)	6 (25)	9 (50)	10 (15)	6 (26)	4 (9%)
Used opioids before, experienced adverse effects				8 (18)	8 (33)	0 (0)[b]	6 (9)	6 (26)	0 (0%)[b]
Read about negative effects				7 (16)	3 (13)	3 (17)	3 (4)	3 (13)	0 (0%)
Heard of negative effects				4 (9)	0 (0)	3 (17)	5 (7)	0 (0)	5 (12%)
Negative experiences of loved one(s)				4 (9)	2 (8)	2 (11)	3 (4)	0 (0)	3 (7%)
Fear of dependence				26 (59)	11 (46)	14 (78)	21 (31)	7 (30)	14 (33)
Against physician's advice				1 (2)	1 (4)	0 (0)	35 (52)	10 (43)	25 (58)
Not being able to drive a car				14 (32)	7 (29)	6 (33)	16 (24)	4 (17)	12 (28)
Use enough medication, don't want more				13 (30)	7 (29)	5 (28)	16 (24)	6 (26)	10 (23)
Breathlessness is not that bad yet				9 (20)	3 (13)	6 (33)	6 (9)	1 (4)	5 (12)
Against advice of loved one(s)				6 (14)	2 (8)	3 (17)	2 (3)	0 (0)	2 (5)
Fear of increase of breathlessness				4 (9)	2 (8)	2 (11)	2 (3)	2 (9)	0 (0)
Used opioids before, didn't help				4 (9)	4 (17)	0 (0)	0 (0)	0 (0)	0 (0)
Fear of imminent death				3 (7)	0 (0)	3 (17)	0 (0)	0 (0)	0 (0)
My religion doesn't allow using opioids				1 (2)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Other				3 (7)	3 (13)	0 (0)	1 (1)	0 (0)	1 (2)

Notes: Data are presented as n or n (%). [a]: six patients didn't know if they had used opioids before and are therefore excluded from this stratified analysis. [b]: $p<0.01$ for difference between patients who had used opioids before and patients who had never used opioids. **Abbreviation:** NA: not applicable.

Data were described using mean±SD or median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. We compared the willingness to use opioids between sexes, age (<65 years or ≥65 years), educational level (lower education, defined as having finished secondary vocational education versus higer education, defined as having finished at least Higher General Secondary Education),[13] diagnosis and mMRC score (<2 or ≥2 points) using Chi-squared test or Fisher-Freeman-Halton test, as appropriate.

Between November 2018 and May 2019, 237 patients were eligible and 175 patients (50% male), median age 65 years (IQR 57 to 70 years), completed the survey (response rate 74%). Patients were diagnosed with COPD (n=124, 71%), CHF (n=18, 10%), asthma (n=17, 10%), interstitial lung disease (n=8, 5%), COPD-asthma overlap syndrome (n=3, 2%), pulmonary hypertension (n=3, 2%) and other (n=2, 1%). Median mMRC score was 2.5 points (IQR 2 to 3 points), 6MWD was 393±107 m and 141 (81%) patients completed lower education only. Nonresponders were 45% male and aged median 66 years (IQR 59 to 71 years; both p>0.05 compared to responders).

72 (41%) out of 175 patients previously used one or more different opioids (49 [68%] for pain, 10 [14%] for breathlessness, eight [11%] for both pain and breathlessness, five [7%] for drug dependence and six [8%] for unknown reasons). Opioids used were morphine (n=45, 63%), oxycodone (n=30, 42%), fentanyl (n=7, 10%), methadone (n=6, 8%) and buprenorphine (n=3, 4%). At the time of the survey, 14 (8%) out of 175 patients used an opioid (seven [50%] for pain, five [36%] for breathlessness, one [7%] for both pain and breathlessness and one [7%] for drug dependence). Six (43%) patients used morphine, four (29%) patients used fentanyl, four (29%) patients used oxycodone and one (7%) patient used methadone. Median daily morphine equivalent dose was 27.5 mg (IQR 16.25 to 30.00 mg) with an outlier of 480 mg (dependence).

In total, 64 (37%) patients were willing to use opioids for breathlessness, 44 (25%) patients were unwilling and 67 (38%) patients were indecisive. Patients unwilling to use opioids were older compared to patients willing to use opioids and indecisive patients (66 versus 63 and 62 years, respectively; p<0.01). Sex, educational level, diagnosis, mMRC score and previous opioid use were comparable between groups (p=0.79, p=0.06, p=0.42, p=0.06 and p=0.07, respectively).

Main reasons to use opioids were on physician's recommendation (89 [68%] out of 131) and doing as much as possible to feel better (79 [60%] out of 131). Main reasons not to use opioids were concerns about adverse effects (49 [44%] out of 111) and fear of dependence (47 [42%] out of 111). Differences existed between decisive patients and indecisive patients (Table 1). Free-text considerations were not being familiar with opioids, fear of getting high and fear of weight increase.

This study assessed attitudes towards opioid treatment in patients with chronic breathlessness with or without an indication for palliative treatment with opioids. The results showed that attitudes towards opioids are mixed, with only a quarter of the patients unwilling to use opioids. These results do not correspond with physicians' assumptions, who indicate that they do not prescribe opioids because patients are resistant [6]. Three-quarters of the indecisive patients indicated that they rely on physicians' positive advice, and one-third indicated that thet rely on negative advice. So the physician is an important source of information, and open and honest communication is important.[8] Since physicians state that they are insecure in prescribing opioids because of a lack of knowledge,[6,8] more emphasis should be on educating physicians about when and how to treat breathlessness with opioids.

The main barriers against and reasons to use opioids mentioned in this study were consistent with previous studies.[7-9] Concerns related to adverse effects and fear of dependence are the main reasons not to use opioids or to be indecisive. Qualitative studies show that patients experience that small improvements in breathlessness can have a big impact on the quality of life,[9] which fits with the attitude of being willing to do as much as possible.

This study's results have also shown that there are as many opinions as people, which also applies to the way patients gather information to form this opinion. Therefore, a proper provision of information for patients using different channels is necessary.

Low-dose opioids appear to be effective and safe in patients with severe chronic breathlessness.[14-16] However, adverse effects might occur.[15] Therefore, physicians and patients should discuss benefits and possible harms when considering low dose opioids.

A limitation of this study is that the convenience sample consisted of only 175 patients referred to one centre. Another limitation is that not all included patients had an indication for opioid treatment. However, there was no difference in attitude between patients with mild (mMRC<2) and severe breathlessness, indicating that forming an opinion about opioids is irrespective of breathlessness severity and therefore information should be suitable and accessible to all patients with chronic breathlessness. Nevertheless, opioids should be reserved for patients with chronic breathlessness, persisting despite optimal pharmacological and non-pharmacological treatment.[17,18]

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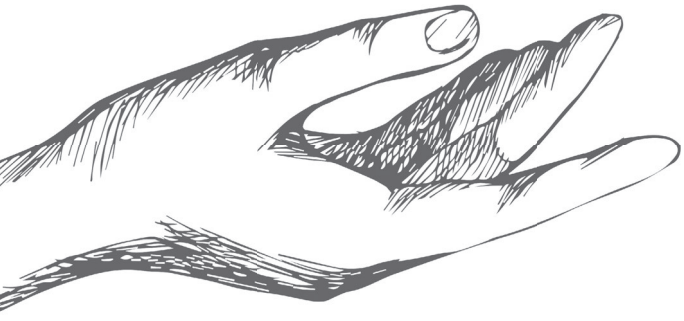

CHAPTER 9

General discussion

Part of the general discussion is published as:

Adverse respiratory effects of opioids for chronic breathlessness: to what extent can we learn lessons from chronic pain?

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Palliative care is an approach that improves quality of life, provides relief from distressing symptoms and intends neither to hasten nor postpone death. It includes an early identification and correct assessment and treatment of distressing symptoms and complications and support of the patient's wishes and needs. Palliative care is applicable early in the course of illness and requires a multidisciplinary and integrated management.[1,2] As the course of chronic obstructive pulmonary disease (COPD) is unpredictable, with acute deteriorations and no distinct terminal phase, early recognition of palliative care needs and treatment of distressing symptoms is crucial.[2-4] Chronic breathlessness is one of the most common symptoms in patients with advanced COPD and palliation of this distressing symptom is an important treatment goal.[5]

Recently, oral sustained-release morphine was licensed for the management of chronic breathlessness in Australia.[6] However, as described in **chapter 1**, several aspects of low-dose, oral sustained-release morphine remained unclear. Therefore, the central aim of this thesis was to review breathlessness management with low-dose, oral sustained-release morphine. In this chapter, the main findings will be discussed in depth. First, I will discuss the effects of opioids in patients with advanced COPD on health-related quality of life and chronic breathlessness. Also, I will discuss impeccable assessment, the safety profile and the willingness of patients to use opioids. Next, the methodological considerations of this thesis will be discussed. I will conclude with the role of low-dose morphine in palliative care of patients with advanced COPD, including future directions for clinical care and research.

Enhancing quality of life

The most important aim of palliative care is the enhancement of quality of life. Few studies have previously assessed the effect of breathlessness management with opioids on health-related quality of life.[7-11] These studies included small patient populations with different conditions and several only reported the results on health-related quality of life in words. Therefore, no meta-analysis could be performed.[12,13] Of these studies, three reported no effect on quality of life,[7,8,10] one reported a beneficial effect[9] and one reported a negative effect.[11] Last year, one of the largest randomized controlled trials (RCT) assessing the effect of opioids on chronic breathlessness was published. Currow et al.[14] treated 284 patients with moderate to very severe chronic breathlessness (modified Medical Research Council [mMRC] breathlessness grade 2 to 4) due to several conditions with 20 mg oral sustained-release morphine or placebo for seven days. Secondary outcome was the effect on health-related quality of life, assessed by the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire Core 15 PAL.[15] Results showed no effect on health-related quality of life. The *MORDYC study*

assessed the effect of 20 to 30 mg oral sustained-release morphine for four weeks in 111 patients with COPD and moderate to very severe chronic breathlessness (mMRC grade 2 to 4, **chapter 4**). Results showed a significant and clinically relevant improvement of health-related quality of life, as assessed by the COPD Assessment Test (CAT, **chapter 5**).[16,17] This effect was only reached after four weeks; no significant or clinically relevant improvement was seen after one or two weeks. As the majority of previous clinical trials only lasted for two weeks or less, it can be questioned if these studies lasted long enough to properly assess the effect of breathlessness improvement on quality of life.[7-10,14] The only study so far with a follow-up longer than four weeks was the study by Poole et al.[11], who studied low-dose, oral sustained-release morphine treatment for six weeks in 16 patients with advanced COPD. Results showed no effect on the total score or the dyspnea, fatigue or emotional subscales of the Chronic Respiratory Disease Questionnaire (CRQ).[18] The mastery subscale in the morphine group slightly deteriorated, while the scores in the placebo group improved, leading to a significant and clinically relevant difference favoring placebo. However, the included patient population was small and the baseline CRQ scores were unknown.

Interestingly, when reviewing the effects on health-related quality of life in the *MORDYC study* on item level, the significant and clinically relevant effect was mainly driven by an improvement on the item 'walking the stairs or hill'. As suggested in **chapter 5**, it is possible that patients experienced an improvement in breathlessness and seized the opportunity to be more active in daily life until they reached a similar level of breathlessness. As patients experience difficulty accepting that daily activities, their independence and their role in a family changes when breathlessness worsens, small changes can have big impact on quality of life.[19-21] However, this was not reflected in the measures of functional performance included in the *MORDYC study* – the 6 Minute Walk Test (6MWT), Care Dependency Scale (CDS) and Timed Up&Go (TUG) test. It can be questioned if these measures are suitable measures to capture the effect of morphine treatment in this population. Previously, patients with moderate to very severe COPD indicated walking, household activities and stair climbing most frequently as problematic daily life activities. Patients were the least satisfied with the performance of dressing/undressing, transfers and showering and bathing.[22] Of these, only walking and transfers are captured by the 6MWT and the TUG test. The CDS captures several of these activities (mobility, dressing/undressing, hygiene and household activities). However, the CDS is designed for patients in nursing homes, who are care dependent in daily life to a certain extent. The population included in the *MORDYC study* was generally not care dependent at baseline, leaving no room to improve. Therefore, monitoring meaningful activities over the day in combination with the level of breathlessness would be more insightful to assess the combined effect of morphine on breathlessness, health-related quality of life and functional performance.

Relief of chronic breathlessness

Data on the effect of opioid treatment on breathlessness remain conflicting. Indeed, insufficient knowledge of positive effects and lack of expertise were the main barriers reported by physicians.[21,23,24] While moderate-level evidence showed that opioids significantly reduce chronic breathlessness,[12,13,25,26] recently this evidence has been brought into question. Meta-analyses have indicated a standardized mean difference of 0.28 to 0.36, corresponding to an effect of 0.52 to 0.66 points on a 0-10 numeric rating scale (NRS) when using the baseline standard deviation of the *MORDYC study*. These meta-analyses included a wide range of patient populations with their severity of breathlessness ranging from moderate to very severe. In patients with COPD the most consistent evidence was shown for opioids given at steady state with a standardized mean difference of 0.42 (corresponding to 0.77 points on the 0-10 NRS).[13] Although these results were significant, they were not considered clinically relevant.[27] Recently, Currow et al.[14] showed no effect on their primary outcome 'breathlessness now' or the secondary outcomes mean, worst or best breathlessness in the previous 24 hours. The magnitude of the effects was less compared to the results of the meta-analyses, which can in part be explained by the fact that the use of rescue medication was allowed in both the morphine and the placebo group. The *MORDYC study* showed a magnitude of effect similar to the meta-analyses on mean and worst breathlessness in the previous 24 hours (**chapter 5**). Both the *MORDYC study* and the study by Currow et al.[14] performed a subgroup analysis in the patients with mMRC grade 3 or 4, although these analyses were underpowered. Where Currow et al.[14] showed a trend for improvement in worst breathlessness, the *MORDYC study* showed a significant and clinically relevant improvement of worst breathlessness and a trend for improvement of mean breathlessness.

Few studies have been performed on the effect of other opioids or routes of administration on chronic breathlessness. The studies on other opioids were mainly small and only dihydrocodeine showed a beneficial effect.[12] Recently, Ferreira et al.[28] studied the effect of 15 mg oral, controlled-release oxycodone for seven days in 155 patients with different conditions and showed no effect on intensity of 'breathlessness now', unpleasantness of 'breathlessness now', or intensity of worst, best or mean breathlessness. Even, the placebo group showed better results on all outcomes except for worst breathlessness. Although the study was underpowered and the use of rescue medication in both the oxycodone and placebo group was allowed, the authors concluded that oxycodone does not improve chronic breathlessness. Furthermore, meta-analyses have consistently demonstrated no effect of nebulized opioids on breathlessness.[12,13,25] Recently, Janowiak et al.[29] assessed the effect of 2.0% nebulized morphine. Breathlessness improved in 11 patients with COPD after four days. However, since they did not assess systemic uptake, a central effect cannot be excluded. Therefore, until now evidence shows the

best implications for oral morphine in the management of chronic breathlessness. As was shown in a dose increment and pharmacovigilance study, an effect of oral morphine should be observed after one week and upward titration until 30 mg per day within one week may be needed.[30,31] When no improvement is observed at 30 mg per day, treatment should be stopped.

Although oral morphine treatment does not improve breathlessness to a clinically relevant extent at group level, it has been suggested that several patient characteristics are related to a positive response.[32,33] *First,* a pooled analysis of effectiveness studies with different patient populations has identified worse breathlessness intensity as a possible characteristic of positive response,[32] with an odds ratio of 1.04 on a 0 to 100 visual analogue scale. Smaller studies were not able to identify breathlessness intensity as a relevant characteristic.[30,33] The *MORDYC study* also showed an association between response to morphine and worse breathlessness intensity (**chapter 6**). For each point increase in breathlessness intensity on a 0 to 10 NRS, the odds of a positive effect increased with 1.55, which is similar to the pooled analysis.[32] Also, as discussed above, both the *MORDYC study* and the study by Currow et al.[14] showed more improvement in breathlessness in the subgroup of patients with mMRC grade 3 or 4. Therefore, breathlessness intensity should be taken into account when considering morphine treatment for breathlessness.
Second, younger age was suggested as possible characteristic. Two smaller studies that dichotomized age with 75 years as cut-off point found no association between age and response to opioid treatment.[30,33] Subsequently, a large pooled analysis identified younger age as predictor when included as continuous outcome.[32] The *MORDYC study* could not confirm these results, which was possibly due to a lack of power, but showed a similar magnitude of effect (**chapter 6**). For each year of aging, the odds of a positive effect to morphine treatment decreases with 1.04 to 1.08. It can be questioned if this is an effect of the process of ageing or the existence of long breathlessness trajectories that comes with age. Perception of breathlessness is influenced by priors, formed by experiences and learned behaviors.[34,35] When breathlessness trajectories are long established, strong priors have been formed.[36] This process of anticipatory learning is associated with less responsiveness to morphine therapy.[37] When considering morphine treatment for breathlessness, age should be considered. Also, the association between response, age and breathlessness trajectories should be studied in a future study.
Third, a favorable effect is suggested in patients describing breathlessness as air hunger,[32,38] but not as breathing work/effort.[39] However, as patients with different conditions choose different descriptors for their breathlessness,[40-42] the attribution of sensory description on a beneficial response to morphine in COPD is unclear. In the *MORDYC study* none of the descriptors of breathlessness could be indicated as predictor of a beneficial response to morphine (**chapter 6**), which is probably due

to a lack of power. Responders to morphine treatment chose air hunger as most accurate descriptor, while non-responders chose various descriptors. This could indicate air hunger as a predictor of positive response to morphine in COPD, which should be examined in a properly powered study.
Fourth, as stated in **chapter 1**, negative affective states such as anxiety and depression can amplify the perception of breathlessness.[43] A small study indicated that opioid responsiveness is decreased when anxiety or depression worsens, even with subtle worsening.[37] As is known from opioid treatment for pain, anxiety or depression can lead to dose escalation and difficulty with tapering off treatment.[44] The presence of anxiety or depression was not reported in the *MORDYC study* and other studies concerning opioids for breathlessness.[12,14] Therefore, the association between responsiveness to morphine for breathlessness and anxiety or depression should be studied in a future study. When this association is confirmed, symptoms of anxiety or depression should be managed first before considering morphine treatment for breathlessness.
Finally, the *MORDYC study* indicated higher body mass index (BMI) as a strong predictor for a beneficial response (**chapter 6**). As morphine metabolism decreases with increasing weight, the positive association might be due to increased levels of morphine metabolites.[45-47] Also, as patients with overweight or obesity show an increased perception of breathlessness compared to patients with normal weight, patients with overweight or obesity might have more room to improve.[48,49] However, since this study was the first study to indicate BMI as characteristic related to a beneficial response to morphine and the explanations are only hypothetical, the relationship and the underlying mechanism should be further studied.

Impeccable assessment

As described in **chapter 1**, measurement of breathlessness can serve different purposes, of which we addressed the purpose of evaluation of the effectiveness of an intervention over time. Breathlessness is a multidimensional symptom involving different mechanisms and pathways.[50] Therefore, a unidimensional measure of breathlessness might not be justified in measuring the effectiveness of morphine on breathlessness.[51,52] Therefore, in addition to mean breathlessness, worst breathlessness and breathlessness unpleasantness should be assessed.[51] Patients with worse breathlessness have more room to improve. Morphine might have the most revealing effect on the active moments during the day, which is reflected in the measure of worst breathlessness. Patients refer to this as 'the edges are off'. When only the average breathlessness during the day is assessed, these peak moments might be faded out and the effect of morphine might then be harder to assess.[20,21] In the *MORDYC study* worst baseline breathlessness showed an improvement in patients with mMRC grade 3 or 4, where mean breathlessness only showed a trend

(**chapter 5**), indicating the need to assess both aspects of breathlessness. Also, as intensity and unpleasantness can vary independently,[50] both dimensions should be assessed. Limbic areas like the hippocampus and amygdala are activated when an efferent-afferent mismatch arises, areas in which opioid receptors are abundantly present. In healthy volunteers, the strong opioid remifentanil interfered with both breathlessness pathways and the process of anticipatory learning, leading to an effect on breathlessness unpleasantness but not on breathlessness intensity.[53] Currow et al.[14] showed a trend for improvement of breathlessness unpleasantness in the subgroup of patients with mMRC grade 3 or 4.

A second important dimension of breathlessness assessment is the beneficial effect on daily life. Results of the *MORDYC study* suggested that patients are able to do more in daily life before reaching a comparable level of breathlessness (**chapter 5**). This was not reflected in the used assessments of functional performance. As both breathlessness and physical activity patterns fluctuate over the day,[54,55] continuous and direct assessment of meaningful daily life activities and symptoms is more appropriate.[56] Activity monitoring would be a proper measurement of physical activity patterns during the day. This simple and noninvasive assessment would give more insight in changes of daily life activities.[57,58] Activity monitoring can subsequently be combined with Ecological Momentary Assessment (EMA).[59] EMA is a method to obtain momentary accounts of symptoms, activities or quality of life. When EMA is used on an electronic device, patients are asked to answer questions on this device on random moments during the day. This combination allows to give insight in real-time symptom burden and the effect of morphine treatment. Also, collected data are not subject to recall bias and give insight in the breathlessness and daily activity patterns of patients in their natural environment.[60] Although EMA has not been applied for breathlessness assessment, it is used to assess the fluctuation in fatigue[61] or applied in rehabilitation for chronic illnesses.[62]

Safety

Both physicians and patients mention fear of serious adverse effects as a major barrier of opioid treatment.[19-21,23,63-65] A retrospective observational study performed in Canada suggested that new opioid prescription has been associated with increased emergency department visits and 30-day mortality in patients with COPD, regardless of opioid dose.[66] However, data on patients who received opioids as palliative treatment were excluded. Also, as this was an observational study, there is no information on cause or effect. The increased risk for emergency department visits and mortality may as well be a marker of disease severity: patients who receive opioids have higher symptom burden and are therefore just more ill. Actually, a large registry study in patients with advanced oxygen-dependent COPD found

no association between low dose opioids (≤30 mg oral morphine equivalent) and hospital admission or mortality after four years of follow-up.[67]

Within morphine treatment, serious adverse effects mainly concern the occurrence of respiratory depression. Fear of respiratory depression is not restricted to treatment of breathlessness, but is also mentioned as barrier in and probably originates from experiences in pain treatment.[23] In COPD, ventilatory responses to hypercapnia and hypoxia are abated,[68,69] which can even be obtunded by opioids.[70] Evidence on respiratory adverse effects of low-dose opioid treatment for chronic breathlessness is limited and conflicting. The respiratory outcomes most reliable to assess respiratory depression are partial arterial pressure of carbon dioxide ($PaCO_2$) and partial arterial pressure of oxygen (PaO_2).[71] Systematic reviews assessing the effect of opioids on breathlessness have indicated no effects on $PaCO_2$, partial end-tidal pressure of carbon dioxide ($P_{ET}CO_2$) or arterial oxygen saturation (SaO_2), but meta-analyses were not conducted. Also, the included studies reported no cases of respiratory depression.[12,13,72] On the contrary, observational studies have reported five cases of respiratory depression in patients treated with opioids for breathlessness.[73-75] Three cases were reported in an observational study to the effect of subcutaneous oxycodone for pain and/or breathlessness. The mean dose reported was 44.6 mg per day (oral morphine equivalent 133.8 mg per day), but the specific dose or indication of the patients that experienced a respiratory depression was not mentioned.[74] The fourth case was in a patient treated for cancer-related pain with 30 mg continue-release morphine per day needing additional treatment for breathlessness with nebulized morphine.[73] The fifth case was a patient treated with 15 mg sustained-release morphine who additionally used a high dose of immediate-release morphine.[75]

To systematically assess the occurrence of respiratory adverse effects of opioids when prescribed for chronic breathlessness, we performed a systematic review and meta-analysis (**chapter 2**). In line with previous systematic reviews, this review showed that there was no evidence of clinically relevant respiratory adverse effects. However, the quality of the included studies was low, the studies were small and used a variety of treatment regimens and patient populations, and the studies were not designed to examine the safety of opioids**.** Further, several included studies assessed the occurrence of a respiratory depression, but did not quantify which outcomes were used to assess a respiratory depression.

Only a few of the studies in **chapter 2** included relevant respiratory outcomes and none of the studies were powered to assess these outcomes. The *MORDYC study* included $PaCO_2$ as primary outcome and 13 other respiratory outcomes as secondary outcome, including outcomes on overnight oximetry and lung function parameters (**chapter 4**). Also, the study included a larger study population and had a longer duration compared to the majority of included studies in **chapter 2**. The results, as described in **chapter 5**, showed that respiratory rate decreased without

a change in $PaCO_2$ or any of the other respiratory outcomes. In a subgroup-analysis in patients with mMRC grade 3 or 4, none of the included outcomes changed.
Currow et al.[14] also assessed respiratory adverse effects, albeit as secondary outcome, and found no effects of morphine treatment on respiratory rate, peripheral oxygen saturation (SpO_2) and $P_{ET}CO_2$. Results of our systematic review, the *MORDYC study* and the study by Currow et al.[14] are of comparable magnitude and similar direction. These results indicate that no clinically relevant differences in alveolar ventilation occur after low-dose morphine treatment.
Another concern is the effect of opioids on respiration during sleep, including central sleep apnea, hypoventilation and oxygen desaturation.[70] Within opioid treatment for pain, a dose-response relationship was shown with the apnea-hypopnea index. The majority of the patients received high-dose opioids.[76,77] It is not known if this conclusion can be drawn for low-dose opioids as well.[78] A recent overview of Cochrane reviews of opioid therapy for chronic pain found no case of respiratory depression, sleep apnea or sleep-disordered breathing.[79] Since the effect in patients with COPD was unknown, we included overnight pulse oximetry in the *MORDYC study*. Results showed no effect on the time SpO_2 was below 90% nor the mean SpO_2 during the night (**chapter 5**). These results are consisted with the Cochrane review on opioids for chronic pain[79] and are indicative for the dose-response relationship. Hence, these results emphasize the relationship between high-dose opioids and increased risk for serious adverse effects and therefore warrant to distinguish between low- and high-dose opioid treatment and confine treatment for chronic breathlessness to low-dose opioids.

Not only respiratory adverse effects, but also gastrointestinal adverse effects as nausea and vomiting, constipation and drowsiness are a concern of morphine treatment.[63,65] Indeed, low-dose morphine treatment comes with several adverse effects.[12,13,43] A systematic review and meta-analysis showed that patients using opioids are 4.7 times more likely to experience nausea and vomiting, 3.0 times more likely to experience constipation and 2.9 times more likely to experience drowsiness.[12] Adverse effects were generally mild, as only 12 patients across all studies dropped out. In the *MORDYC study*, the number of participants experiencing adverse effects was not different between the groups, although the severity of constipation was worse in the morphine group (**chapter 5**). Five participants in the morphine group and one participant in the placebo group had to withdraw from the study due to adverse effects including constipation, nausea, vomiting, dizziness and hallucinations. Currow et al.[14] showed similar results, although participants in the morphine group reported more often and more severe constipation and vomiting. In all studies the adverse effects resolved quickly after termination of the intervention or treatment of the symptom. These results clearly indicate that adverse effects occur in morphine treatment, but are mild and responsive to symptom treatment.

Cost-effectiveness

As breathlessness in the palliative phase of a disease might be difficult to control, healthcare utilization increases. As discussed in **chapter 1**, breathlessness burden is associated with healthcare costs. When breathlessness burden increases, healthcare utilization might increase as well as was shown previously.[80-83] However, these studies were retrospective or cross-sectional studies and used claims data or long recall periods. Our prospective study using patient-reported data with a short recall period confirmed these results (**chapter 3**). This study showed that in patients with high breathlessness burden despite optimal treatment of advanced COPD, healthcare and non-healthcare costs were higher compared to patients with low breathlessness burden. The main cost driver in patients with high breathlessness burden in the first year after pulmonary rehabilitation was hospitalization, indicating that these patients often attend the hospital, with corresponding high costs. The main cost driver in the second year was pulmonary rehabilitation, indicating that when controlling breathlessness with arbitrary interventions fails, a second pulmonary rehabilitation program is initiated. In the view of these high healthcare-related costs of high breathlessness burden, assessment of cost-effectiveness of palliative interventions should be a regular and significant component when interventions demonstrate to be effective. However, assessing all relevant costs in palliative care is challenging, as informal care is a major component of palliative care.[84] To date, cost-effectiveness analyses for palliation of chronic breathlessness are scarce and limited to holistic breathlessness support services.[85,86] In **chapter 7** we conducted a cost-effectiveness analysis of low-dose, sustained-release oral morphine, which showed that four weeks morphine treatment decreased both healthcare and societal costs. As morphine treatment improved health-related and general quality of life, the intervention showed to be cost-effective. This simple and inexpensive intervention reduced healthcare and societal costs within a foreseeable period, which is an important aspect of the effectiveness of morphine treatment. We also showed that conducting a cost-effective analysis in palliative care along a RCT is feasible and therefore encourage others to assess cost-effectiveness of palliative interventions.

Willingness of patients

Unwillingness of patients to use opioids is mentioned as one of the reasons restraining physicians from prescribing opioids.[63] As described in **chapter 5**, the major challenge of the *MORDYC study* was the unwillingness of patients to participate. Due to disappointing recruitment rates, inclusion criteria were expanded to mMRC grade 2 to 4. This was also the case in the study by Currow et al.[14] Main reasons for unwillingness of patients eligible to participate in the *MORDYC study* were related

to morphine (28%) and to the burden of the project (24%). Barriers to start opioid treatment have been reported before. Small qualitative studies indicate fear of dependence and fear of imminent death as most important barriers.[19-21] However, these studies were mainly conducted in patients with experience with opioid treatment[21] or in patients that agreed to participate in an opioid-trial.[20] We assessed these reasons for willingness or unwillingness to start opioid treatment in a survey among patients with chronic lung or heart disease, as described in **chapter 8**. The patients surveyed did not necessarily have an indication for opioid treatment for breathlessness and were not necessarily informed by a physician about opioids. About one third of patients surveyed was willing to use opioids for breathlessness and another one third was indecisive. In line with previous studies, main barriers were concerns about adverse effects and fear of dependence, where the main reason to start opioids was to do as much as possible to feel better.[19-21] Fear of imminent death was only mentioned by three patients. Important result of the survey was that the physician plays an important role in the decision of patients. For indecisive patients, recommendation of their physician is the most important reason to start opioid treatment and a negative advice of their physician is the most important reason not to start. These results were irrespective of previous opioid use, sex, educational level, diagnosis and breathlessness burden. This indicates that proper information and communication by physicians and shared decision making is very important. To overcome the physicians' lack of knowledge and expertise, proper education and information should be emphasized.

One of the barriers reported was the fear of dependence,[19-21] which is a legitimate concern given the opioid epidemic surrounding over-prescription and drug-misuse of opioids for pain management. As patients live with chronic breathlessness for many months or years, misuse may occur. Should we use the lessons learned from the world of analgesics when considering opioid treatment for chronic breathlessness? A systematic review published in 2015 concluded that for some harms, including dependence, "higher opioid doses are associated with increased risk".[87] With analgesia, high doses and dose escalation titrating against severity of pain are usual practice, but patients with breathlessness are usually treated with low-dose opioids (≤30 mg oral morphine equivalents a day[30]). Therefore, it is questionable whether the knowledge of analgesia can be extrapolated to the treatment of chronic breathlessness with low-dose opioids. Responders in a long-term effectiveness study (mean of 209.5 patient-days per participant) used a mean of 14 mg per day, of which only 7.7% used the highest dose of 30 mg per day to gain benefit.[30] In participants needing a dose increment up to 30 mg per day to gain benefit, improvement continued without further dose titration over the following seven days, a phenomenon not described in pain response.[31] However, although the doses for breathlessness treatment are lower than doses associated with dependence, intended or unintended misuse can still occur.[75,88] Misuse is less likely with morphine compared to other opioids[89] and with sustained-release opioids

compared to immediate-release opioids.[90] Therefore, sustained-release morphine treatment should be the first choice opioid for breathlessness treatment. Also, proper and timely monitoring of patients is important to prevent misuse.
Not being able to drive a vehicle was one of the main reasons patients declined to participate in the *MORDYC study* and was also indicated as a barrier in **chapter 8**. Driving is an activity related to freedom and independence for many adults, especially when being single.[91] For patients with COPD, driving is also essential to attend therapy or go to a doctor's appointment.[92,93] Due to possible adverse effects as dizziness, patients are advised against driving during therapy initiation or upward dose titration. Where high doses can impair driving,[94] patients receiving stable low-dose morphine and their caregivers don't experience impairment of driving skills of the patient.[93] However, as this is not assessed in a clinical trial, care must be taken. This issue and the consequences should be discussed by the patient and physician before morphine treatment is initiated.

Methodological considerations

This thesis has several strengths. *First*, we conducted a broad analysis of the effects of low-dose, oral sustained-release morphine. **Chapter 2** gives an overview of the current knowledge on respiratory adverse effects, also including observational studies and case reports. As these studies are closer to daily practice, the results gave insight in what happens and can happen outside laboratory settings. Also, we performed meta-analyses of five respiratory outcomes. The *MORDYC study* (**chapter 4**) was powered to estimate health-related quality of life and respiratory adverse effects. In **chapter 5** we assessed 14 respiratory outcomes, including overnight oximetry. To conclude, we performed a cost-analysis (**chapter 7**), which was the first cost-effectiveness analysis on opioids for breathlessness. *Second*, we included optimally treated patients. Palliative care is indicated in patients experiencing breathlessness refractory to disease-modifying management.[95] Patients in **chapters 3**, **5**, **6 and 7** all recently completed a comprehensive pulmonary rehabilitation program, ensuring state-of-the-art pharmacological and nonpharmacological management.[96] This enables the generalizability of results to patients to whom this palliative management of breathlessness is intended. *Third*, we conducted a thoroughly-conducted cost-analysis of COPD and of morphine treatment. Both **chapter 3** and **chapter 7** included the healthcare and societal perspective. Breathlessness has a major impact on the daily life of patients,[97,98] placing more burden on informal caregivers.[82,99] Covering all cost aspects of breathlessness gives a proper overview of the consequences of this distressing symptom and the effects of its management. Also, results were grounded by several sensitivity analyses. *Finally*, the *MORDYC study* was one of the first RCTs with a study duration of more than one week.[12,13] This enabled us to increase the treatment dose after one week,

as is usual in clinical practice. Also, it enabled us to show the impact of morphine on health-related quality of life. Although it is only theoretical, this gave insight in the combined effect on breathlessness, functional ability and quality of life.

This thesis has several limitations which should be considered when interpreting the results. *First*, we did not reach the intended sample size of 124 participants for the *MORDYC study*. Of the patients that consented to participate, thirteen patients dropped out between consent and study start. In the majority of patients this was because of recurring acute exacerbations of COPD, for which some were prescribed morphine. *Second*, the sample size calculation of the *MORDYC study* was based on two of the assessed outcomes, the CAT for assessing health-related quality of life and $PaCO_2$ for assessing impact on respiratory outcomes. The study was therefore not powered to assess the other outcomes. Breathlessness was not included as primary outcome, as at trial design several systematic reviews indicated that morphine improves breathlessness. However, a large RCT published after completion of the *MORDYC study* brought this into question.[14] Also, the study was not powered to determine the interaction between severity and description of breathlessness and response to morphine. The five known descriptors of breathlessness could only be included in the regression analysis one by one. Also, only age, breathlessness severity and BMI could be included. *Third*, **chapters 3 and 7** were based on several assumptions. Although the costs questionnaires were designed to the best knowledge at the time of study design, not all information was gathered. In **chapter 3**, assumptions had to be made regarding transportation and employment status. To minimize missing data, we contacted patients to complement the questionnaires, but this was not possible in each patient. *Finally*, although the *MORDYC study* was one of the longest studies to date, long-term effects, adverse effects and cost-effectiveness remain unknown. The only medium- or long-term data to date are from observational studies that have shown that the benefit of low-dose morphine was maintained for three months in one-third of patients[30] and that low-dose opioids are not associated with increased hospital admissions rates or mortality.[67,100] Data on long-term cost-effectiveness are lacking.

Conclusions and future directions

This thesis has indicated the prominent role of low-dose, oral sustained-release morphine in the palliation of chronic breathlessness in patients with advanced COPD.

For clinical practice, this thesis has the following implications. *First*, low-dose, oral sustained-release morphine has a prominent place in palliative breathlessness management, as it enhances quality of life, relieves breathlessness in part of the

patients, is safe and is cost-effective. As the sustained-release formulation induces the lowest peaks and highest troughs, this formulation will lead to the least adverse effects and is therefore the preferred formulation. However, when not available, immediate-release formulations at a fixed schedule can be prescribed as well.[101] An effect should be perceived within one week.[30,31] When no effect is perceived, treatment dose can be increased up to 30 mg per day in intervals of one week. When a patient perceives no effect at the maximal dose of 30 mg or perceives intolerable adverse effects, the treatment should be stopped. *Second*, a broader assessment of breathlessness is indicated. Up until recently, only breathlessness in general was used to assess the effectiveness of morphine treatment. However, breathlessness is a multidimensional symptom and these different dimensions should be taken into account. Results have shown worst breathlessness and breathlessness unpleasantness are more responsive to morphine treatment compared to mean breathlessness. *Third*, as patients can live with chronic breathlessness for years and the long-term effectiveness and safety profile is still unclear, morphine treatment should only be considered as palliative treatment in patients whose breathlessness remains severe (mMRC grade 3 or 4) and refractory to optimal treatment of the COPD. As response is also more likely in younger patients, age should be taken into account as well. *Fourth*, physicians and patients should always discuss the possible benefits and harms when considering low-dose morphine. When preferred, loved ones should be involved in this conversation. Patients primarily rely on the information and recommendation of their physician. However, each patient gathers information in their own way. Therefore, proper information should be available, suitable and accessible via different channels to all patients with chronic breathlessness. *Finally*, when the joint decision is made to start morphine treatment, proper monitoring of the effect is crucial. This also accounts for upward dose titration. Although adverse effects are generally mild and the occurrence of respiratory adverse effects is minimal, it is unknown in which patients they occur.

Although this thesis has given insight in several aspects of low-dose, oral sustained-release morphine, some aspects remain unclear. Future research should therefore focus on the mechanism in which morphine improves breathlessness and improves health-related quality of life. Based on the results of the *MORDYC study*, we hypothesized that improvement of breathlessness leads to the ability to do more in daily life, which improved quality of life. However, this is only a theory, which should be confirmed in a future study including measures to monitor symptom fluctuation and daily activities.

In addition, the role of several patient characteristics in COPD remains unclear, including age, sensory description of breathlessness, BMI and symptoms of anxiety and depression. These characteristics should be investigated in more detail, in order to give the right treatment to the right patient. For age, it should be determined if the possible disadvantageous response in older age originates in the process of

ageing or in established priors. Different sensory descriptors should be addressed to determine if air hunger is indeed a predictor of response in COPD. As the *MORDYC study* was the first study to indicate increased BMI as a characteristic associated with beneficial response, this association should be confirmed in a well-powered study. The association with symptoms of anxiety and depression and a disadvantageous response to morphine should be mapped.

Lastly, the long-term effectiveness, safety profile and cost-effectiveness remain unclear. Therefore, a study with a longer follow-up should be considered.

When designing a future RCT, the following aspects should be taken into account:

- Given the low willingness of patients to participate in a morphine-trial, a multicenter trial is recommended;
- When assessing the effect on breathlessness, including a multidimensional set of outcomes with at least mean breathlessness, worst breathlessness and unpleasantness of breathlessness is recommended;
- When assessing the interplay between breathlessness, daily life activities and health-related quality of life, continuous and direct assessment of these outcomes, for instance by means of activity monitoring in combination with Ecological Momentary Assessment, is recommended. This continuous and direct assessment enables researchers to link changes in daily life activities to changes in breathlessness and quality of life in the patient's natural environment.

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ADDENDA

Summary

Chronic breathlessness is a common symptom in patients with advanced chronic obstructive pulmonary disease (COPD) with major consequences. Opioids have been suggested as effective palliative treatment for chronic breathlessness, with the best evidence for low-dose, oral sustained-release morphine. Palliative care is an approach that improves quality of life, provides relief from distressing symptoms and intends to neither hasten nor postpone death. Several of these aspects are unclear for low-dose, oral morphine. The effects on quality of life, breathlessness, functional performance and respiratory outcomes remain conflicting. Also, prospective data on the long-term economic burden of chronic breathlessness are scarce, as are data on long-term effectiveness and cost-effectiveness of oral morphine treatment. Therefore, the main aim of this thesis was to provide a comprehensive understanding of the effects of low-dose, oral morphine for breathlessness. In addition, we have given insight in the economic burden of chronic breathlessness and the willingness of patients towards use of opioids for breathlessness (**chapter 1**).

In **chapter 2** a systematic review and meta-analysis were performed to study the respiratory adverse effects of opioids for chronic breathlessness. Several databases were searched for studies that assessed the effect of opioids on respiratory outcomes. We included original research articles such as randomized controlled trials, nonrandomized trials, case-control studies, cohort studies, chart reviews, case reports and case studies. We assessed six outcomes: arterial carbon dioxide tension ($PaCO_2$), arterial oxygen tension (PaO_2), arterial oxygen saturation (SaO_2), respiratory rate, end-tidal carbon dioxide tension ($P_{ET}CO_2$) and occurrence of respiratory depression. Meta-analyses were performed using randomized data for all continuous outcomes. We included 63 articles describing 67 studies. The meta-analysis showed a statistically significant, but clinically irrelevant increase in $PaCO_2$ in patients using opioids for breathlessness compared to placebo. No other significant changes were shown in the meta-analyses or the other included studies. A respiratory depression occurred in four patients after a high or unknown opioid dose. Based on these results, we concluded that low-dose opioids do not cause clinically relevant respiratory adverse effects. However, the included studies used a heterogeneity of study designs and the quality was low, indicating the need for a larger, adequately powered study.

Healthcare utilization in patients with COPD increases with increasing disease severity and the presence of comorbidities. However, the impact of breathlessness burden on healthcare utilization and daily activities is unclear. In **chapter 3**, the impact of breathlessness burden on healthcare utilization and economic burden is assessed. This observational study followed patients with COPD for 24 months

after completion of a comprehensive pulmonary rehabilitation program. Every three months, participants completed a cost questionnaire, covering healthcare utilization, employment status and impact on daily activities for both breathing problems and other health problems. The results were compared between participants with low (modified Medical Research Council [mMRC] breathlessness grade <2) and high breathlessness burden (mMRC grade ≥2). Main cost drivers for the total study population were hospitalizations, contact with other healthcare professionals (mainly physiotherapists) and pulmonary rehabilitation. Patients with high breathlessness burden showed higher costs for inpatient care, pulmonary rehabilitation and informal care compared to patients with low breathlessness burden. This study highlights the relevance of adequate breathlessness relief in order to reduce healthcare utilization and economic burden of patients with COPD.

While the effect of opioids on health-related quality of life and respiratory adverse effects remained unclear, the *MORDYC study* was designed (**chapter 4**). This single-center, randomized, double blind, placebo-controlled intervention study assessed the effect of low-dose, oral, sustained-release morphine in 124 patients with COPD and moderate to very severe chronic breathlessness despite optimal treatment of their COPD. These patients were randomly assigned to either 10 mg morphine or placebo twice daily for four weeks, with the possibility to increase to three times daily after one or two weeks in patients who did not experience a clinically relevant improvement of breathlessness. Assessed outcomes were disease-specific health-related quality of life, respiratory outcomes, functional performance, breathlessness, adverse effects and costs.

Chapter 5 describes the results of the *MORDYC study* on health-related quality of life, respiratory outcomes, functional performance, breathlessness and adverse effects. Health-related quality of life improved statistically significant and clinically relevant in the morphine group compared to the placebo group. Respiratory outcomes, functional performance and breathlessness remained unchanged. In the subgroup of patients with severe to very severe breathlessness (mMRC grade 3 or 4), worst breathlessness improved, while other outcomes remained unchanged. No serious adverse effects occurred. These results showed that four weeks treatment of low-dose, oral sustained-release morphine may improve disease-specific health-related quality of life in patients with COPD and moderate to very severe breathlessness, without affecting respiratory outcomes or causing serious adverse effects. Breathlessness improved in patients with severe to very severe chronic breathlessness.

Not all patients experience a clinically meaningful improvement of breathlessness from morphine treatment. The aim of **chapter 6** was to assess the relationship between a beneficial response to morphine treatment, sensory breathlessness

description and demographics using the results of the *MORDYC study*. Higher baseline breathlessness and higher body mass index were associated with a beneficial response to morphine, while age and the sensory breathlessness descriptors were not. Morphine treatment should therefore be considered in patients with COPD with severe breathlessness. As this was the first study indicating body mass index as a predictor, this relationship should be further studied.

High breathlessness burden is associated with increased healthcare utilization and healthcare-related costs. Adequate breathlessness relief in order to reduce economic burden in patients with COPD and severe chronic breathlessness is therefore relevant. The aim of **chapter 7** was to analyze the cost-effectiveness of regular, low-dose morphine using the data of the *MORDYC study*. Both healthcare and societal costs were higher in the placebo group compared to the morphine group. As quality of life improved, morphine treatment was dominant from a healthcare perspective and from a societal perspective. Several sensitivity analyses substantiated these results. Based on these results, we concluded that low-dose, oral morphine for four weeks is cost-effective regarding the healthcare and the societal perspective.

Although opioids are recommended for patients with optimal pharmacological and nonpharmacological treatment of the underlying causes of breathlessness, physicians experience barriers to prescribe opioids. One of the barriers mentions by physicians is the resistance of patients. This can limit effective palliative treatment of breathlessness. In **chapter 8**, we assessed the willingness to start opioid treatment in 175 patients with chronic lung or heart disease, irrespective of a current indication for opioid treatment. Attitudes towards opioid treatment were mixed, with one quarter of patients being unwilling to start opioid treatment. Of the remaining patients, half of the patients was willing to use opioids and half of the patients was indecisive. Willingness was only related to age, with older patients more often being unwilling to use opioids. The main reason to be unwilling was fear of adverse effects and the main reason to be willing was to do as much as possible to feel better. The physician is an important source of information for indecisive patients. So, proper provision of information for patients is necessary. Patients and physicians should discuss the benefits and possible harms when considering low-dose opioids.

Finally, in **chapter 9** the main findings of this thesis were discussed in depth in relation to previously published studies. We have concluded that low-dose, oral sustained-relief morphine treatment has a prominent role in the palliation of chronic breathlessness in patients with advanced COPD. Morphine enhances health-related quality of life, is safe and is cost-effective. In addition, morphine relieves breathlessness in part of the patients and should therefore be considered in patients with severe to very severe breathlessness. Patients and physicians should always

discuss the benefits and possible harms of treatment before initiation in order to make a joint decision. However, not all aspects of morphine treatment are evident. Therefore, future studies are crucial in order to assess the long-term effectiveness and cost-effectiveness and to further explore characteristics associated with a beneficial response.

Samenvatting

Chronische kortademigheid is een veelvoorkomende klacht bij patiënten met gevorderde COPD en heeft grote psychische en sociale gevolgen. Opioïden worden beschouwd als effectieve palliatieve behandeling van chronische kortademigheid, met de beste resultaten voor lage dosis orale morfine met langdurige afgifte. Palliatieve zorg heeft als doel kwaliteit van leven te verbeteren en symptoomlast te verminderen, zonder de dood uit te stellen of te versnellen. Uit eerdere studies bleek dat voor lage dosis orale morfine verschillende van deze aspecten van palliatieve zorg onduidelijk zijn. Zo zijn het effect op kwaliteit van leven, kortademigheid, fysiek functioneren en respiratoire parameters (uitkomtmaten van longfunctie- en bloedonderzoek) tegenstrijdig. Daarnaast is onduidelijk wat de economische impact van chronische kortademigheid op de lange termijn is en of morfine kosteneffectief is. Tot slot zijn de lange-termijn effectiviteit en kosteneffectiviteit van morfine niet bekend. Daarom is het belangrijkste doel van dit proefschrift om een uitvoerig beeld te geven van de effecten van lage dosis orale morfine. Daarnaast geef ik inzicht in de economische impact van chronische kortademigheid op de lange termijn en de bereidheid van patiënten om opioïden te gebruiken voor kortademigheid (**hoofdstuk 1**).

In **hoofdstuk 2** beschrijven we een systematische review en meta-analyse die we hebben uitgevoerd om de effecten van opioïden voor chronische kortademigheid op respiratoire parameters in kaart te brengen. In diverse databases is gezocht naar studies die de effecten van opioïden op respiratoire parameters hebben gemeten. Hierbij hebben we originele studies geïncludeerd, zoals gerandomiseerde interventiestudies, niet-gerandomiseerde interventiestudies, case-control studies, cohortstudies, dossierstudies, case reports en casestudies. We keken naar 6 parameters: koolstofdioxidedruk in arterieel bloed ($PaCO_2$), zuurstofdruk in arterieel bloed (PaO_2), zuurstofsaturatie in arterieel bloed (SaO_2), ademfrequentie, koolstofdioxidedruk in de uitgeademde lucht ($P_{ET}CO_2$) en het optreden van een ademdepressie. Meta-analyses zijn uitgevoerd met data uit de gerandomiseerde interventiestudies voor alle continue uitkomstmaten. We includeerden 63 artikelen, waarin 67 studies werden beschreven. Uit de meta-analyse kwam naar voren dat $PaCO_2$ statistisch significant toenam bij patiënten die opioïden gebruikten voor kortademigheid in vergelijking met placebo. Deze toename was echter niet klinisch relevant. Op de andere parameters werd zowel in de meta-analyses als in de overige studies geen significant effect gezien. Bij 4 patiënten werd een ademdepressie gerapporteerd. Zij werden echter behandeld met een hoge of onbekende dosis opioïden. Op basis van deze resultaten kunnen we concluderen dat een lage dosis opioïden niet leidt tot klinisch relevante respiratoire bijwerkingen. Echter, de geïncludeerde studies gebruikten verschillende methoden, wat de vergelijking

moeilijk maakt. Daarnaast was de kwaliteit van de studies vaak laag. Daarom is er behoefte aan een grotere en langere studie.

Bij patiënten met COPD neemt het zorggebruik toe wanneer de ernst van de ziekte toeneemt en bij de aanwezigheid van meer aandoeningen dan alleen de COPD (comorbiditeiten). Het is tot nu toe onduidelijk wat de invloed is van de ernst van kortademigheid op zorggebruik en op dagelijkse activiteiten. Daarom hebben we dit in **hoofdstuk 3** vastgesteld. In deze observationele studie zijn patiënten met COPD 24 maanden gevolgd na het afronden van een longrevalidatieprogramma. Elke drie maanden vulden deze patiënten een kostenvragenlijst in. Daarin werd gevraagd naar zorggebruik en het kunnen uitvoeren van werk en dagelijkse activiteiten. Vervolgens werd gevraagd of dit een gevolg was van hun ademhalingsproblemen of van eventuele andere gezondheidsproblemen. De resultaten werden vergeleken tussen patiënten met milde (modified Medical Research Council [mMRC] graad 0 of 1) en ernstige kortademigheid (mMRC graad 2 tot 4). In de totale patiëntengroep waren ziekenhuisopnames, contact met overige zorgprofessionals (met name fysiotherapeuten) en longrevalidatie de belangrijkste kostenposten. Patiënten met ernstige kortademigheid hadden hogere kosten voor intramurale zorg, longrevalidatie en informele zorg in vergelijking met patiënten met milde kortademigheid. De andere kostenposten waren gelijk voor patiënten met milde en ernstige kortademigheid. Deze studie toont aan dat het belangrijk is om kortademigheid te verlichten, zodat zorgkosten worden verminderd.

Aangezien het effect van opioïden op gezondheid-gerelateerde kwaliteit van leven en op bijwerkingen op de ademhaling onduidelijk was, is de *MORDYC-studie* opgezet (**hoofdstuk 4**). De *MORDYC-studie* was een single-center, gerandomiseerde, dubbelblinde, placebogecontroleerde interventiestudie. Het doel van de studie was het vaststellen van het effect van lage dosis orale morfine met langdurige afgifte bij 124 patiënten met COPD en matige tot zeer ernstige kortademigheid (mMRC graad 2 tot 4), ondanks optimale behandeling van de COPD.
Deze patiënten werden willekeurig verdeeld over een groep die behandeld werd met tweemaal daags 10 mg morfine of een groep die behandeld werd met placebo. Patiënten werden voor vier weken behandeld. Bij patiënten die geen klinisch relevante verbetering van hun kortademigheid ervaarden na een of twee weken kon de dosering opgehoogd worden naar driemaal daags. Uitkomstmaten van de studie waren het effect op ziekte-specifieke kwaliteit van leven, respiratoire parameters, fysiek functioneren, kortademigheid, het optreden van bijwerkingen en kosten.

Hoofdstuk 5 beschrijft de resultaten van de *MORDYC-studie* op ziekte-specifieke kwaliteit van leven, respiratoire parameters, fysiek functioneren, kortademigheid en het optreden van bijwerkingen. In de totale studiegroep verbeterde de kwaliteit van leven significant en klinisch relevant in de morfinegroep in vergelijking met

de placebogroep. De respiratoire parameters, het fysiek functioneren en de kortademigheid bleven gelijk in beide groepen. Daarnaast werd ook gekeken naar de effecten van lage dosis morfine in een subgroep van patiënten met ernstige tot zeer ernstige kortademigheid (mMRC graad 3 of 4). In deze groep verbeterde de ergste kortademigheid over de dag in de morfinegroep in vergelijking met de placebogroep, terwijl alle andere uitkomsten gelijk bleven. In de studie werden geen ernstige bijwerkingen vastgesteld. De resultaten van de *MORDYC-studie* laten zien dat behandeling met lage dosis orale morfine met langdurige afgifte voor vier weken de ziekte-specifieke kwaliteit van leven kan verbeteren bij patiënten met COPD en matige tot zeer ernstige kortademigheid, zonder te leiden tot ernstige bijwerkingen. De kortademigheid verbeterde alleen bij de subgroep van patiënten met ernstige tot zeer ernstige kortademigheid.

Eerder onderzoek heeft laten zien dat niet alle patiënten een klinisch relevante verbetering van de kortademigheid ervaren na behandeling met morfine. Het doel van **hoofdstuk 6** was om de relatie vast te stellen tussen een klinisch relevante verbetering, de manier waarop de patiënt het gevoel van kortademigheid omschrijft en demografische eigenschappen van de patiënt. Dit werd gedaan met behulp van de resultaten van de *MORDYC-studie*. Hieruit bleek dat ernstigere kortademigheid aan het begin van de studie en een hogere body mass index samenhangen met een klinisch relevante verbetering van de kortademigheid. De leeftijd van de patiënt en de manier waarop het gevoel van kortademigheid omschreven wordt hingen niet samen met een klinisch relevante verbetering. Daarom zou behandeling met morfine alleen overwogen dienen te worden bij patiënten met COPD en ernstige kortademigheid. Aangezien dit de eerste studie was die body mass index als voorspellende eigenschap aantoonde, dient deze samenhang verder onderzocht te worden.

Ernstige kortademigheid hangt samen met de toename van zorggebruik en zorgkosten. Om de economische impact van patiënten met COPD en ernstige kortademigheid te verminderen is een goede behandeling van kortademigheid belangrijk. Het doel van **hoofdstuk 7** was om de kosteneffectiviteit van lage dosis orale morfine met langdurige afgifte vast te stellen. Dit werd gedaan met behulp van de resultaten van de *MORDYC-studie*. Hieruit bleek dat zowel de zorgkosten als de maatschappelijke kosten hoger waren in de placebogroep in vergelijking met de morfinegroep. Kwaliteit van leven verbeterde, waardoor morfinebehandeling dominant was vanuit een gezondheidszorgperspectief en een maatschappelijk perspectief. Verschillende sensitiviteitsanalyses bevestigden deze resultaten. Op basis van deze resultaten concluderen we dat lage dosis orale morfine met langdurige afgifte kosteneffectief is vanuit zowel het gezondheidszorgperspectief als het maatschappelijk perspectief.

Opioïden worden aanbevolen voor patiënten die ondanks een optimale behandeling van hun COPD kortademigheid ervaren. Toch ervaren artsen barrières om opioïden voor te schrijven. Een van de barrières die zij benoemen is weerstand van de patiënt. Dit kan optimale palliatieve behandeling beperken. In **hoofdstuk 8** hebben we de bereidheid van patiënten om te starten met opioïdenbehandeling in kaart gebracht. 175 patiënten met een chronische longaandoening of hartaandoening werden gevraagd naar hun bereidheid, onafhankelijk van een indicatie voor deze behandeling. De houding ten aanzien van opioïdenbehandeling was wisselend. Een kwart van de patiënten was niet bereid om opioïden te gebruiken. Van de overige patiënten was de ene helft bereid om opioïden te gebruiken en de andere helft had hier geen duidelijke voorkeur in. Alleen de leeftijd van de patiënt hing samen met de bereidheid om opioïden te gebruiken, waarbij oudere patiënten vaker niet bereid waren om opioïden te gebruiken. Angst voor bijwerkingen was de belangrijkste reden om niet bereid te zijn om opioïden te gebruiken. De belangrijkste reden om wel bereid te zijn was om zo veel als mogelijk te willen doen om zichzelf beter te voelen. Patiënten die geen duidelijke voorkeur hadden, gingen vooral af op het advies van hun arts. Daarom is passende informatievoorziening aan patiënten noodzakelijk. Wanneer een behandeling met lage dosis opioïden overwogen wordt, is het belangrijk dat de patiënt en de arts gezamenlijk de voordelen en nadelen van de behandeling bespreken.

Tot slot worden in **hoofdstuk 9** de belangrijkste bevindingen van dit proefschrift uitgebreid besproken in relatie tot eerder gepubliceerde studies. Hierin concluderen we dat lage dosis orale morfine met langdurige afgifte een prominente rol speelt in de palliatieve behandeling van chronische kortademigheid bij patiënten met gevorderde COPD. Morfine verbetert de gezondheid-gerelateerde kwaliteit van leven, is veilig en is kosteneffectief. Daarnaast verlicht morfine kortademigheid bij een deel van de patiënten. Daarom zou lage dosis morfine altijd overwogen moeten worden bij patiënten met gevorderde COPD en ernstige tot zeer ernstige kortademigheid. De patiënt en de arts dienen altijd de voordelen en mogelijke nadelen van de behandeling gezamenlijk te bespreken voordat de behandeling wordt gestart, zodat een weloverwogen gezamenlijke keuze gemaakt kan worden. Echter, niet alle aspecten van morfinebehandeling zijn tot op heden duidelijk. Daarom zijn toekomstige studies belangrijk om het effect en de kosteneffectiviteit op lange termijn vast te stellen en om verder in kaart te brengen welke patiënten een klinisch relevante verbetering van de kortademigheid ervaren na behandeling met morfine.

Scientific and social impact

This thesis has provided several findings, which contribute to science and medical practice. This paragraph reflects on the scientific and social impact of this thesis, which will be discussed from four different perspectives:

- *Research:* What is the main aim of the included studies and what are the main results and conclusions?
- *Relevance:* What is the (potential) contribution of the scientific results to science and to social sectors and challenges?
- *Target groups:* To whom are the scientific results favorable and/or relevant and why?
- *Activities:* In which way can the identified target groups be involved in and informed about the results, so that the knowledge can be used in the future?

Research and relevance

Breathlessness is one of the most common symptoms reported by patients with advanced chronic obstructive pulmonary disease (COPD), a chronic condition in which the lungs are inflamed and damaged. This stressful symptom has major consequences for the patients, such as care dependency, social limitations and anxiety. With worsening of the breathlessness, patients experience more difficulties in performing daily life activities, more anxiety restricting them to their house and growing dependence on loved ones. As COPD can have an irregular course, breathlessness and the accompanying problems shift over time with ups and downs. Also, worsening of breathlessness over time leads to increasing contacts with physicians or admissions to the hospital. This increase in medical care induces an increase in healthcare related costs. Therefore, effective treatment of chronic breathlessness is important. Opioids are suggested as effective palliative treatment for chronic breathlessness. Palliative care aims to provide relief from stressful symptoms and to improve quality of life, without curing the underlying disease. Within the group of opioids, low-dose, oral morphine with prolonged release has shown the best effect in relieving breathlessness.

The main aim of this thesis was to provide an extensive summary of the benefits and harms of low-dose, oral morphine. The results have shown that low-dose, oral morphine for four weeks improves quality of life in patients with advanced COPD without causing serious side effects. Also, patients taking low-dose, oral morphine for four weeks were shown to have fewer contacts with healthcare providers and lower healthcare related costs compared to patients taking placebo. Therefore, low-dose, oral morphine has an important role in the palliative treatment of chronic breathlessness in patients with advanced COPD. Finally, the results of this thesis showed that some patients are willing to use opioids for breathlessness, but some patients are not. The main reason to be willing to use opioids is to do as much as possible to feel better. The main reason to be unwilling to use opioids is

fear of serious side effects. When patients are indecisive, they mainly rely on the information from their physician. Physicians should know about the positive effects of morphine and the possible harms, so they can inform patients and their informal caregivers about the treatment.

Target groups

Multiple groups benefit from the results of this thesis. Patients directly benefit from morphine treatment. As relief of breathlessness can also decrease the care dependency of patients, morphine treatment will also benefit the informal and formal caregivers of patients. This thesis provides information for physicians about the positive effects and possible harms of low-dose oral morphine use, which can aid them to inform patients and informal caregivers. Also, the results are relevant for future researchers, since some aspects of low-dose morphine treatment remain unclear.

Healthcare providers

Healthcare providers experience barriers to prescribe morphine treatment for breathlessness. These barriers include insufficient knowledge of the positive effects, fear of side effects and resistance of patients. Effects of opioid treatment on breathlessness and on quality of life were unclear. Also, it was known that morphine relieves breathlessness in some patients, but not in all patients, and it was unclear which patient characteristics are related to a positive response. These issues are discussed in this thesis. The results show that low-dose, oral morphine improves quality of life without causing serious side effects. Also, the results show that patients with worse breathlessness are more likely to respond to morphine treatment. This can aid physicians to identify to which patients they should prescribe low-dose, oral morphine. When morphine treatment is started, the effect of the treatment should be monitored. Physicians should ask patients about different breathlessness aspects, like average severity and unpleasantness of breathlessness over the last 24 hours and worst breathlessness severity in the last 24 hours. Since patients indicate that they rely on the information given by their physician, it is important that healthcare providers know about the effects and side effects of low-dose oral morphine treatment and gain experience with the treatment. These healthcare providers include chest physicians, family doctors, physicians in old age medicine, physician assistants and nurse specialists.

Patients

Patients directly benefit from morphine treatment, as it improves quality of life. Patients indicate to be willing to use opioids for their breathlessness, but also indicate to have some concerns. The results of this thesis contributed to a better understanding of patients' concerns related to morphine use. The main concern of patients is the occurrence of side effects. This thesis has determined the occurrence

of side effects and has shown that no serious side effects occur after treatment with low-dose morphine. Patients report that their physician is the most important source of information when considering opioid treatment. Therefore, patients should be aware of the benefits and possible harms of morphine treatment so they can start a conversation about their specific concerns with their physician.

Researchers

This thesis has indicated several aspects important to future research. As a start, results indicate that worse breathlessness is related to a positive response to morphine treatment. Therefore, only patients with severe to very severe breathlessness (modified Medical Research Council [mMRC] breathlessness grade 3 or 4) should be included in future studies. However, given that we have shown that it is difficult to include patients with mMRC grade 3 or 4 in the MORDYC study, we recommend a multi-center set up in future studies.

This thesis has also raised several questions. Morphine improves health-related quality of life, but no improvement in breathlessness was shown. The working mechanism of morphine should be further explored, focusing on the interplay between breathlessness, quality of life and daily life activities. Also, the influence of age, body mass index, the way breathlessness is described and the presence of anxiety or depression on a positive response to morphine treatment should be further explored.

Activities and products

Several activities have been undertaken to spread the results of this thesis to healthcare providers, patients and researchers. As a start, the results have been published in international, peer-reviewed journals and have been presented at different national and international congresses and meetings. This will be undertaken with results in the future as well. Also, local, national and international media have paid attention to the main results of the *MORDYC study*. The results were presented in the Medicine News (Medicijnjournaal) of the Dutch Institute for Rational Use of Medicine. The results were also reported on the website of the Dutch Lung Foundation.

In order to support the information provision to patients, we developed an infographic. This infographic will be available for general practitioners, chest physicians and other healthcare providers to share with their patients and informal caregivers. The infographic informs patients and their informal caregivers about the effects of morphine for chronic breathlessness and helps patients to start a conversation with their physician.

Finally, the findings of the *MORDYC study* are included in the revision of the Dutch guideline *Palliative care for COPD*, which will be published in 2021. The revision of this guideline was initiated by the Netherlands Comprehensive Cancer Organization and Lung Alliance Netherlands. The revised guideline is developed by

a multidisciplinary working group consisting of several healthcare providers and patient representatives. The guideline contains recommendations for healthcare providers based on the current scientific knowledge and medical practice. Several future activities will be performed to implement this guideline and therefore also the results of this thesis. These activities include: articles in newsletters of relevant professional associations and education to several healthcare providers in order to raise awareness of the guideline, the development of a decision tree to aid healthcare providers in provision of palliative care to patients with advanced COPD and the development of a patient version of the guideline, which will be spread on several patient platforms.

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It's something unpredictable, but in the end it's right,
I hope you had the time of your life

Liefs,

About the author

Cindy was born on April 25, 1988 in Eindhoven, the Netherlands. After completing secondary education (gymnasium) at Jacob Roelandslyceum in Boxtel, she studied Biomedical Sciences at Radboud University, Nijmegen. In 2009, she obtained her bachelor's degree and in 2011 her master's degree in Clinical Human Movement Sciences. During her master, she followed an extracurricular minor on rehabilitation sciences at KU Leuven, Belgium and did an internship at the department of physiotherapy at Karolinska Institutet, Sweden.

After her graduation, Cindy was employed at the client contact center of a housing company. During this period, she also contributed to several research projects at the department of rehabilitation at the UMC St. Radboud, Nijmegen and the department of pediatric rehabilitation at the St. Maartenskliniek, Nijmegen. In 2015, Cindy started her PhD at the department of Health Services Research of the CAPHRI Care and Public Health Research Institute of the Maastricht University, in collaboration with Ciro, Horn and the Center of Expertise in Palliative Care of Maastricht UMC+. Her research focused on the management of chronic breathlessness with low-dose morphine in patients with advanced COPD, which included the benefits, adverse effects and cost-effectiveness of low-dose morphine and the attitudes of patients regarding opioid treatment. During her PhD, Cindy followed courses on, among others, Cochrane systematic reviews, trial-based and model-based economic evaluations and multilevel analysis of longitudinal data. The results of her research were presented on several national and international congresses. In November 2020, Cindy won the annual palliative care research prize of the Center of Expertise in Palliative Care Amsterdam for her article *Effect of sustained-release morphine for refractory breathlessness in COPD on health status; a randomized controlled trial*.

Currently, Cindy is employed as an advisor in palliative care at the Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland, IKNL), where she is responsible for the process management of multidisciplinary palliative care guidelines.

Scientific publications

Scientific articles in international journals

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Submitted articles

Verberkt C.A., van den Beuken-van Everdingen M.H.J., Schols J.M.G.A., Wouters E.F.M. and Janssen D.J.A. Predictors of response to morphine for chronic breathlessness in chronic obstructive pulmonary disease: a cross-sectional study.

Conference contributions

Verberkt C.A. Respiratoire bijwerkingen van opioïden bij kortademigheid. 2017. Oral presentation, *Verenso najaarscongres*, Ede, the Netherlands.

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