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palliative care in copd widening the scope

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PROLOGUE

Prologue, general introduction
a short history of palliative care in COPD and outline of the thesis

PROLOGUE: THE SILENT CHEST

Between 2005 and 2012, I was in training as a pulmonologist. I encountered patients with all kinds of lung diseases, but chronic obstructive pulmonary disease (COPD) was the most prevalent. I learned to interpret pulmonary function tests and thoracic imaging. I read articles on whether inhaled corticosteroids were indicated (this has always been a hot topic for pulmonologists). I learned to consider three important treatment options for patients with severe COPD: pulmonary rehabilitation, lung volume reduction therapy and lung transplantation. But these options still left us with a lot of patients with a high burden ofdisease.

In those years, encountering a person with severe COPD often made me feel empty-handed. I was glad (I hate to confess this) when an exacerbation turned out to be a secondary pneumothorax - at least I could do something. The more patients I saw, the more I realized that our knowledge was hardly ever useful to them. It was mostly helpful to us, healthcare professionals: we could categorize the phenotype and severity of COPD, we could decide whether a chest CT was necessary, we had thoughts on prescribing inhaled corticosteroids or not. But where was the patient? For example, if there was no reason for inhaled corticosteroids, I would stop it, but what if the patient said: 'This inhaler makes me feel safe, why must I switch?' And what if the forced expiratory volume was significantly less than last time, but my patient felt better? What was I going to say? Why did I do the test in the first place? And when my patient left the office, what was that nagging feeling that important things were left unsaid? Because I could guess that my patient was anxious, or even depressed, but what could I do?

In those years, it seemed as if most pulmonologists had silently agreed that end-stage COPD (severe airflow obstruction, high symptom burden and no disease-modifying options) was a lost cause. On top of that, the patient advocacy group has never been strong - possibly due to low health literacy and smoking-related stigma. In other words, most pulmonologists were silent, and most patients were silent too - like their ominous 'silent chest'.

Fortunately, other healthcare professionals let themselves be heard. They were palliative care physicians, elderly care physicians, nurses and other healthcare providers who had a broad scope on illness (such as those working in primary care and in rehabilitation medicine). And they produced a steadily growing body of research, which showed that palliative care interventions in COPD - such as holistic breathlessness management and advance care planning - potentially had a positive impact on quality of life.

Possibly, the fact that most research was not initiated by pulmonary medicine is reflected in the arduous implementation of palliative care in pulmonary outpatient clinics. And due to how they were trained, pulmonologists tend to have a 'somatic scope' on COPD, which may be a barrier in delivering holistic palliative care. However, together with general practitioners and elderly care physicians, pulmonologists are still the ones that are usually responsible for the care of patients with COPD.

Taking all this into account, a critical look at our own pulmonary practice is called for. The historical models of COPD care do not meet the demands of those with end-stage disease. We should continue to search for practical interventions to improve their quality of life, with resourcefulness and compassion.

GENERAL INTRODUCTION

Definition and early days of the palliative care movement

The World Health Organization defines palliative care as an approach that improves the quality of life of patients and their loved ones, who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of physical, psychosocial and spiritual problems[1].
In the 1960s, palliative care was the response to the end-of-life care needs of patients with advanced cancer. In those early days, the movement was closely linked to the hospice movement. It was not until 1987 that palliative medicine was acknowledged as a subspecialty of general medicine in the UK [2]. The focus of palliative care would remain on malignant diseases until around the turn of the millennium, when the first articles on palliative care in chronic organ failure were published[3-7]. The great Dame Cicely Saunders, the founder of the hospice movement, acknowledged herself in 2001 that this oncological scope had "hindered the acceptance in other challenges of need. But," she wrote four years before her death, "how do we balance need, skills and resources?" [8].

Treatment options for COPD

Chronic Obstructive Pulmonary Disease (COPD) is a common, incurable disease characterized by airflow obstruction, emphysema and chronic bronchitis [9]. Breathlessness is the most common symptom in COPD.
Before the turn of the millennium, advanced COPD was not yet associated with palliative care. However, patients' poor quality of life and prognosis became obvious in two landmark papers on the effectiveness of long-term oxygen therapy (LTOT) in the early 1980s. The Medical Research Council trial showed that five-year survival of hypoxemic COPD patients (younger than 70 years at enrollment) with versus without LTOT was 55% and 33%, respectively (10). One year earlier, the Nocturnal Oxygen Therapy trial found that disturbances in emotional and social functioning were common and that patients experienced a severe impairment in activities of daily living [11].
In those years, the only intervention that might be regarded as 'palliative' was pulmonary rehabilitation. Most other strategies that were available classify as disease-modifying interventions (such as smoking cessation, oxygen and bronchodilator drugs).
In the second half of the 1990s, an interesting new option appeared in the literature: lung volume reduction surgery (LVRS)[12]. The rationale for LVRS in patients with heterogenous emphysema is that excision of a part of the lung, usually a destroyed part, diminishes hyperinflation. In terms of palliative versus disease-modifying treatment, LVRS might be regarded as a hybrid. Indeed, the National Emphysema Treatment Trial (NETT) research group was divided over whether their primary endpoint should be length of survival and exercise capacity or palliation, measured by dyspnea and quality of life scores [13]. (The investigators that favored the first option won this battle.) In 2003, when the famous NETT trial (in which 1,218 patients with severe emphysema were randomized to undergo LVRS or usual care) was published, it became clear that patient selection for this intervention was pivotal. As the authors stated, "the functional benefits of LVRS came at the price of increased short-term mortality and morbidity" [14].
In the same year the NETT trial was published, a research letter appeared in the Lancet, claiming that volume reduction could be achieved through bronchoscopic lung volume reduction (BLVR) with endovalves [15]. In the ensuing years, this treatment option would turn out to be of great value for those with severe heterogenous emphysema. Unfortunately, only a minority of patients are eligible. For example, in the Netherlands, only one out of five referred patients are selected to undergo BLVR [16]. Of note, those who are referred already represent a small selection of COPD patients. To put it bluntly, BLVR is for the lucky few. For them, the treatment may have an impressive effect on quality of life and exercise capacity [17]. The other side of the coin, of course, is the great disappointment for those clutching at straws, when they receive the message that they are not eligible for this treatment.

Advance care planning

We return to the year 2003, when the first articles on LVRS and BLVR were published. There was another first that year: a 'Grand Round' article was published, in which a COPD patient's wishes regarding his death were reflected upon - making it the first publication on advance care planning (ACP) in COPD[18]. "Mr. Jan" had end-stage COPD and mild dementia, resided in a nursing home, and had clearly expressed his wishes to both his family and the nursing personnel. Unfortunately, his wishes didn't quite match what happened: full treatment on the ICU, complicated by agitation and self-extubation.
The term ACP had been coined ten years before[19]. In that period, many Americans were confident that the process of completing living wills and appointing proxies would be boosted by the Patient Self-Determination Act (PSDA), that passed in 1990. The PSDA obliged hospitals to inquire upon admission whether a patient had advance care directives. Also, patients should be given written notice of their decision-making rights upon admission. Despite the high hopes many had, the PSDA did not evidently generate a change in care. Indeed, conclusions of the SUPPORT trial (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment), published five years after the act passed, were dispiriting [20]. The study, performed in five teaching hospitals, described the care provided to seriously ill patients who were admitted to the hospital. There was little communication and planning, and symptom control was poor. Furthermore, patients dying with nonmalignant disease received more aggressive interventions (such as resuscitation and treatment on the intensive care unit) than those with cancer.
The SUPPORT trial might be regarded as the beginning of a long and winding road towards integrating ACP in COPD practice. At first, focus was more on 'the product' (advance directives) - later this would shift towards the process of communication. ACP nowadays is not so much about filling out documents (although recording preferences remains pivotal) but has become a more holistic interaction between healthcare provider, patient, and family caregivers. The focus is not just on the last days of life but has broadened to the patient's current goals and preferences. It should be tailored to the patient's level of understanding and personal values. Furthermore, it is not a 'once in a lifetime' conversation, but an ongoing and iterative process, since patient preferences are subject to change. As you can see, the distinction between ACP and high-quality, individualized and empathic communication has become unclear. Because we should always involve family caregivers, we should always have the outlines of a crisis plan (since crises are a natural part of COPD), we should always be curious what is important for our patients apart from the physical domain, we should always adjust to their level of understanding,

and we should always communicate with other healthcare providers what has been decided. And once you have started having this type of conversations, you do not stop. (After you have had a long and openhearted conversation with your neighbor about everything that moves and scares you, you don't go back to: 'Good morning sir, enjoy your day.')

Identification of COPD patients with palliative care needs

Although both the British Thoracic Society and the American College of Chest Physicians acknowledge the importance of ACP for patients with COPD, implementation has been challenging to this day. One of the main barriers is the uncertainty around prognosis [21]. This brings us to another topic that has kept researchers busy: timely identification of COPD patients with palliative care needs.

Historically, palliative care is care for the terminally ill patient [2]. If the patient still has several years to live, palliative care seems inappropriate. Since it is impossible to accurately assess prognosis in COPD, this left us with a catch-22 that lasted for years.

Several tools were developed to identify COPD patients with palliative care needs, leaning heavily on prognosis. It was assumed that there is some transition point, after which it is appropriate to deliver end-of-life services. With cancer, such a 'milestone' may be more easily identified, but the prolonged and unpredictable COPD trajectory demands a different approach. As Kendall et al. stated: "Maybe we need to take a step back, listen to the messages from the extensive qualitative literature and ask ourselves 'if we started with a blank sheet of paper, how would supportive care for people with COPD look?" [22]

The consequences of the struggle to identify 'palliative' COPD patients and to implement appropriate palliative care are worrisome. In several articles, the care given to advanced COPD patients was compared to the care given to those with inoperable lung cancer. (Lung cancer may be used as a 'reference standard' since patients have a relatively similar symptom profile to those with COPD.) A recent meta-analysis found that lung cancer patients receive substantially more formal palliative care, medications for symptom management and less life-sustaining measures compared to people with advanced COPD [23]. Both populations experience distressing symptoms, with a similar prevalence of pain and (probably) more breathlessness in COPD.

So, not for lack of trying, but care provision for COPD remains far behind. Arguably, we have overcomplicated the organization of healthcare by trying to draw a distinction between palliative care and high quality, personalized, appropriate care for people with advanced COPD. Just as we created a distinction between ACP and high-quality communication on everything that matters. Using the term 'palliative care' for COPD has not been helpful per se, since it carries a stigma for both patients and healthcare providers and may provoke fear and avoidance [24], whilst there is no clear 'palliative phase' (as opposed to many cases of cancer). In other words, the notion that we suddenly had to do something new, and renamed what we were doing, may well be our greatest barrier.

Perhaps the solution is not to be found in radical changes of care and renaming things, but in simply ameliorating existing care. By taking more time, by routinely assessing what is important on other domains than just the physical, by anticipating on future scenario's, by involving a multidisciplinary team. Since 'time' is frequently mentioned as another barrier for ACP and palliative care by pulmonologists [25], delegating more responsibility to adequately trained nurses seems an essential step. The effectiveness of nurse-led ACP has been well demonstrated [26]. There is no reason to assume that this effectiveness is any less for the delivery of palliative care for COPD patients in general. Since respiratory nurses have profound knowledge of the disease trajectory and often have longstanding relationships with COPD patients, it is justified to appoint them as central caregiver for those with advanced disease, co-working with general practitioners, elderly care physicians or pulmonologists, and consulting a palliative care consultant when necessary.

Breathlessness management

At this point, you may wonder whether there has been any research on symptom management - or were we just trying to mold our patients into care models? The answer to this question brings us, again, back to the year 2003. Abernethy and colleagues published their landmark study on morphine for breathlessness in patients with life-limiting illnesses, mostly COPD[27]. Thirty-eight patients with severe breathlessness were treated with morphine for four days and had some improvement. There were a few other small studies on this subject with mixed results, but it was generally assumed that morphine was effective for breathlessness.

This period of relative uncertainty lasted until 2020, when three randomized controlled trials were published. These trials demonstrated no significant change in dyspnea for sustained-release morphine and oxycodone [28,29,30]. Of these three, the Dutch "MORDYC" (Morphine for Treatment of Dyspnea in Patients With COPD) trial[30] is the most important trial for our daily practice, since it included only COPD patients and the control group did not use any opioids (as opposed to the studies of Currow et al.[28] and Ferriera et al.[29] in which all arms received short-acting morphine as needed). The MORDYC trial only showed a statistically significant effect on worst daily dyspnea in a subgroup of COPD patients with a modified Medical Research Council (mMRC) ≥ 3. Since then, the communis opinio is that there is only a small role for morphine in the management of refractory severe breathlessness. Some important questions are still unanswered, such as long-term effects, safety, and the effectiveness of opioids such as fentanyl.

If one dives deep into the complexity of breathlessness in advanced COPD, it is perhaps not surprising that drugs will have a slight effect at best. In the last decade, we have been treated to a stream of highly relevant papers on this debilitating symptom. One of the new viewpoints that are highlighted in this body of research, is the patients' individual cognitive and affective responses to breathlessness - explaining the lack of correlation between physiologic disturbances and symptom burden. Valuable contributions from expert patients underscore an aspect of breathlessness that had previously been ignored in literature: the overwhelming experience, which cannot be measured or indeed 'understood' by healthcare professionals. In the words of Carel (patient and professor of philosophy): "Pathological breathlessness descends on you, paralyzing you. Until you get that breath in, nothing else can happen. Nothing else matters. Your world closes in on you and nothing is present except the terrible need to breathe, get more air in and out, and slowly regain control over the panting and panic that have taken over." [31]

It falls upon the shoulders of those caring for patients with advanced COPD (and other life-limiting diseases causing refractory breathlessness) to optimize individually tailored breathlessness management. Obviously, we should not only address the physical, but also the social, the spiritual and the psychological aspects of breathlessness.

Pulmonary rehabilitation may offer a suitable environment for such a breathlessness intervention. It delivers integrated care through a multidisciplinary team, and focusses on specific needs of the individual patient. Although rehabilitation and palliative care have subtly different goals (raising functional status versus symptom relief), the overlap is considerable and integration of the two services might be a way to go[32].
Unfortunately, rehabilitation is not for everybody. Patients may experience personal barriers such as fatigue, anxiety, transportation difficulties, limited privacy and confrontation with severely ill patients. Furthermore, there is limited availability of pulmonary rehabilitation in many parts of the world.
Another promising movement is the formation of holistic breathlessness services. They provide pharmacological and non-pharmacological treatments to patients and family caregivers, across settings, using multidisciplinary approaches. They emphasize self-management, and target improvements in quality of life by reducing the impact of breathlessness and related symptoms on everyday living [33]. Such breathlessness services are almost invariably initiated by palliative care teams, offering an opportunity to integrate COPD care and palliative care.

CONCLUSION

The history of palliative care and COPD appears to be a rather slow struggle to improve care. On the other hand, we should bear in mind that it was only 20 years ago that palliative care for COPD was first considered. We have learned from what have been barriers to improve care. The most important barrier has probably been that palliative care is historically oncology- and hospice-based, which has been throwing quite some sand in our eyes. It usually makes sense to build from what already exists, but in the case of COPD, it would have been better to 'start with a blank sheet of paper'. Judging from the increasing amount of literature on COPD and palliative care, it is evident that this part of care will no longer be ignored. And it is encouraging how much progress has been made on understanding and managing breathlessness.

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis was gathering knowledge on how to improve care for patients with advanced COPD, given on a respiratory outpatient clinic. The research questions arose from our daily practice.

Part one (chapter 2) concerns with the question which COPD patients should be eligible for palliative care.
Part two (chapters 3 and 4) focusses on smoking-related stigma and patient perspectives on home oxygen therapy. Chapter 3 is a qualitative research on patients' perspectives on long-term oxygen. Shame and stigma were an important theme in this study. The theme of smoking-related stigma is explored from the physician's perspective in chapter 4.
Part three concerns with the role of opioids for breathlessness management in severe COPD. Chapter 5 describes a survey amongst Dutch pulmonologists on their willingness to prescribe opioids for refractory breathlessness in advanced COPD. Chapter 6 is a literature review on current evidence for opioids for refractory dyspnea in COPD.
Furthermore, this chapter decribes the study design for a randomized controlled clinical trial, investigating the effectiveness of fentanyl and morphine.
Part four focusses on non-pharmacological breathlessness management in severe COPD. The potential benefits of a close collaboration with a psychologist for COPD patients with combined breathlessness and anxiety are described in chapters 7 (on cognitive behavioral therapy) and 8 (on eye movement desensitization and reprocessing (EMDR)). Chapter 9 describes how we implemented a breathlessness service within a respiratory outpatient clinic. In chapter ten, a summary of results and insights is given, and is placed into current perspective.

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On identification of COPD patients in need of palliative care

Part

Chapter 2

Part A

COPD patients in need of palliative care: Identification after hospitalization through the surprise question

Chron Respir Dis 2018

Dionne Noppe
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ABSTRACT

Currently, few patients suffering from chronic obstructive pulmonary disease (COPD) who might benefit from a palliative care approach are referred to a palliative care team. Tools to identify patients eligible for a palliative care approach have been found to be difficult to apply in daily practice. Therefore, there is need for a simple and easily applicable tool to identify those patients who would benefit from referral to a palliative care team. The aim of this study was to determine if the surprise question (SQ) "Would I be surprised if this patient dies within 12 months?" in a subset of recently hospitalized COPD patients identifies those subjects. Recently hospitalized COPD patients were included, and the answer to the SQ was provided by the treating pulmonologist. The gold standards framework (GSF) prognostic indicator guidance was regarded as the gold standard test and was assessed for each patient. Sensitivity, specificity, and negative and positive predictive values were calculated to determine the accuracy of the SQ plus recent hospitalization compared to the variables of the GSF. A total of 93 patients were analyzed. In 35 patients (38%), the answer to the SQ was "not surprised"; 78 patients (84%) met ≥1 criteria of the GSF (15 (16%) did not meet any criteria). Specificity and positive predictive value for the SQ were both 100% ((78.2-100) and (87.7-100), respectively). Sensitivity was 44.9% (33.7-56.5) and negative predictive value was 25.9% (22.2-29.9). The "not surprised" group fulfilled significantly more GSF criteria. The SQ after recent hospitalization for COPD has a very high specificity compared to a standardized tool and is therefore a useful tool for the quick identification of patients who are most likely to benefit from palliative care. However, this method doesn't identify all patients who are eligible for referral to palliative care.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a progressive disease causing about 7000 deaths in the Netherlands each year, thereby being the fourth leading cause of death.[1] Studies have shown a high symptom burden in patients with end-stage COPD, similar to patients with incurable cancer[2,3] There is now general acknowledgment that optimal care for patients with advanced chronic organ failure such as COPD should be based on an integrated approach with integration of physical, psychosocial, as well as spiritual aspects of care.[4] However, in comparison with care for patients with malignant disease, provision of palliative care for COPD is currently limited.[5]

End-of-life care preferences are rarely discussed by patients and their health care providers and referral to palliative care is often not considered.[6-8] This might be partly due to the unpredictable course of the disease, characterized by stable periods and acute exacerbations. Moreover, a qualitative study showed that in contrast to cancer, there is a lack of understanding in patients that COPD is a life limiting disease, making a discussion about palliative care more challenging.[9]

It has been suggested that hospitalization for an acute exacerbation of COPD (AECOPD) might identify patients who potentially require palliative care,due to high mortality rates and loss of quality of life.[3,10-12] In addition, several instruments have been developed to help clinicians recognize patients who may benefit from palliative care and assess patients' needs. An example of such an instrument is the gold standards framework (GSF) prognostic indicator guidance.[13] Other general identification tools are the supportive and Palliative Care Indicators Tool,[14] andrecently the Necesidades Paliativas Centro Colaborador de la OMS - Instituto Catala´n de Oncologı´a.[15] These tools are well validated, yet complicated and difficult to use in daily practice.[13,16]

The surprise question (SQ; "Would I be surprised if this patient died in the next year?") is a simple tool to trigger the health care professional to consider referral for palliative care.[17,18] The SQ has been incorporated into several guidelines and identifications tools,[19] including the GSF.[13] These instruments warrant further exploration, especially with regard to whether the patient has unmet needs and may benefit from palliative care. However, we hypothesize that after hospitalization forCOPD, the SQcan be used as a screening tool in daily practice to identify patients who are in need of palliative care. This approach might identify patients without the need of collecting clinical data or using a complex algorithm.

To test our hypothesis, we compared the SQ with a reference tool (the GSF) to identify subjects in need of palliative care in a group of patients who have recently been hospitalized for an AECOPD. Our identification tool is referred to as "hospitalization and surprise question" (HSQ).

METHOD

Design and study population

The study was an observational prospective study, conducted at the outpatient clinic of pulmonary medicine in the Spaarne Gasthuis, the Netherlands. The Spaarne Gasthuis is a large community-based teaching hospital with 818 beds. A palliative care team is available for consultation for both inpatients and outpatients.

Inclusion criteria were as follows: (1) known COPD; (2) hospitalization with an AECOPD between 1 January 2016 until 21 May 2017; and (3) an appointment at the outpatient clinic between 1 May and 22 June. A clinical diagnosis of COPD and AECOPD is defined according to the global initiative for chronic obstructive lung disease (GOLD) guideline 2017.[20]

Patients were excluded if they missed their appointment at the outpatient clinic or if their physician felt unable to answer the SQ.

The primary outcome measures were defined as sensitivity, specificity, and negative and positive predictive value of the SQ compared to a set of indicators as stated in the GSF (Table 2.1). Secondary outcome measures were the prevalence of outpatients with GSF criteria and baseline clinical characteristics.

Table 2.1 Variables based on the gold standards framework prognostic indicator guidance.

General indicators
Decreased activity (Karnofsky performance status ≥3)
Severe comorbidity (using Charlson comorbidity index)
Advanced disease
Decreasing response to treatment, decreasing reversibility
Increasing need for support (as reported by the patient or caregivers)
Choice of no further active treatment (do not resuscitate order, no admission to ICU)
Acute/unplanned hospital admissions (≥3 in last 12 months due to COPD)
Progressive weight loss (>10%) in past 6 months
Sentinel event (e.g. serious fall, bereavement, divorce, and retirement due to medical condition)
Serum albumen <25 g/l
COPD specific indicators
FEV1 <30% predicted
Signs or symptoms of right heart failure
Fulfils oxygen therapy criteria
MRC grade 4 or 5 (shortness of breath after 100 m on the level of confined to house)
More than 6 weeks of systemic steroids in the preceding 6 months
Use of NIV during last hospital admission

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; ICU: intensive care unit; MRC: medical research council; NIV: non invasive ventilation.

The GSF contains general indicators and COPDspecific indicators. Patients were as sessed as "GSF1+" if ≥1 variable of the general indicators was met. Due to variation in the cutoff point for a positive score on several prognostic tools available,[15,16,21] we also conducted a stricter analysis for patients being considered GSF+ if they met ≥2 criteria of the GSF was met (GSF2+). Likewise, the cutoff for the indicator"comorbidity" differs from ≥2 or ≥1 comorbidities in some validation studies.15,22 For this reason,we conducted the same analysis but with a cutoff point of ≥2 comorbidities for a positive score on comorbidity (GSFcom2+). For the disease-specific indicators, if ≥2 of these indicators were met, patients were assessed as "advanced disease." "Advanced disease" is one of the general indicators of the GSF. As a consequence, patients meeting ≥2 of the specific clinical indicators were also assessed as GSF1+.

For assessment of comorbidity, we used the ageadjusted Charlson comorbidity index because it is a well validated prognostic measure for illness burden and most commonly used in contemporary clinical research.[23] Karnofsky performance status was used for assessing activities and functional performance status.[24]

Data collection

First, data were obtained from the electronic patient medical records. Baseline characteristics included the following variables:[1] demographic variables,including age and sex, domestic situation (single and living together), place of living (home, residential home, and nursing home), and date of hospital admission for AECOPD; [2] COPD-related variables namely GOLD grade (I–IV, according to version 2014)[25] and smoking history; and[3] measurable variables according to the set of indicators as described in the GSF.

Additional variables were incorporated in a short questionnaire administered at the outpatient visit (Appendix 2.1). Finally, the patients' treating pulmonologist was approached after the appointment at the outpatient clinic to answer the SQ. For all patients included, we used the binary response option (i.e.surprised or not surprised). If the pulmonologist answered "not surprised" to the SQ, the patient was considered SQ+. For the answer "surprised," the patient was considered SQ-. A total of nine pulmonologists were involved in the assessment.

Statistical analysis

The statistical program SPSS version 20 was used to analyze the data. Data were summarized as mean ±SD, median (interquartile range), or count (percentage). To analyze the difference between baseline characteristics, χ^2 test for nominal variables and *t*-test for continuous, normally distributed variables was used. For non-normally distributed continuous and ordinal variables, Mann-Whitney *U* test was used. To analyze variance in answer to the SQ between the pulmonologists, Wilkinson rank sum test was used. Sensitivity, specificity, and positive and negative predictive values of the SQ tool were calculated. A two-tailed ρ-value of ≤ 0.05 was considered statistically significant.

Ethics

Ethics approval was obtained by the local ethics committee of the Spaarne Gasthuis, prior to the start of the study and informed consent was obtained from all patients prior to data collection.

RESULTS

Patient characteristics

Of 743 patients hospitalized with an AECOPD during the period of 1 January 2016 until 30 April 2017, 109 fulfilled the inclusion criteria of having an appointment at the outpatient clinic during the period of May1 and June 22. Median time between hospitalization and assessment was 155 days 25–535. Ten patients missed their appointment at the outpatient clinic, two patients had died and one patient was hospitalized at the time of appointment, leaving 96 evaluable patients all of whom agreed to participate. Of two patients, the involved pulmonologists could not provide an answer to the SQ because these patients were referred to them for the first time and they did not have enough information to conduct a critical assessment. In one patient, the reason for hospital admission was found to be congestive heart failure instead of COPD, and the patient was excluded from analysis. Finally, a total of 93 patients were analyzed.

Of the 93 patients, 35 (38%) were SQ+ (58 SQ-, 62%), and 78 (84%) met the standard referral index of ≥1 criteria of the GSF and were GSF1+ (15 GSF-, 16%). Sixty patients (65%) fulfilled ≥2 criteria of the GSF (GSF2+); 26 (29%) patients had ≥2 comorbidities, 10 (9%) patients had ≥3 comorbidities, with a mean Charlson comorbidity index score of 5. Eleven patients (12%) received PC at time of inclusion. An overview of all baseline characteristics is displayed in Table 2.2. Stratified by the answer to the SQ, SQ+ patients had a significantly lower forced expiratory volume in 1s (FEV_1), higher COPD GOLD class, and higher incidence myocardial infarction in their medical history. SQ+ patients did significantly fulfill more GSF criteria than SQ- patients. Furthermore, in the SQ+ group, there were significantly more patients receiving PC at the time of inclusion. Overall comorbidity and all other baseline characteristics, except smoking, did not differ significantly. Variance in answer to the SQ did not differ significantly between the nine pulmonologists.

Table 2.2 Baseline characteristics stratified by binary surprise question response.[a]

	Total cohort ($n = 93$)	SQ+ ($n = 35$)	SQ− ($n = 58$)	*p*-Value
Age, y	71 (69–73)	73 (70–75)	70 (68–73)	0.20
Sex				
Male	41 (44)	17 (49)	24 (41)	0.50
Female	52 (66)	18 (51)	34 (59)	
Ethnicity				
Caucasian	93 (100)	35 (100)	58 (100)	
Condition of living				0.19
Married/living together	57 (61)	25 (71)	32 (55)	
Living with children	2 (2)	1 (3)	1 (2)	
Living alone	34 (37)	9 (26)	25 (43)	
Place of living				1
Home	90 (97)	34 (97)	56 (96)	
Nursery home	2 (2)	1 (3)	1 (2)	
Rehabilitation center	1 (1)	0 (0)	1 (2)	
Smoking history				0.002
Current smoker	25 (27)	3 (9)	22 (38)	
Past smoker	68 (73)	32 (91)	36 (62)	
COPD GOLD class				<0.001
1	4 (4)	1 (3)	3 (5)	
2	28 (30)	1 (3)	27 (46)	
3	40 (43)	17 (49)	23 (40)	
4	21 (23)	16 (45)	5 (9)	
FEV1 (%)	45 (42–49)	37 (33–40)	51 (47–55)	<0.001
Time since last hospital admission	155 (68–313)$^{\Sigma}$	166 (59–329)$^{\Sigma}$	147 (72–303)$^{\Sigma}$	0.84
Number of AECOPD without HA	1 (0–3)	2 (1–2)	1 (0–3)	0.43
Number of HA	1 (1–2)	1 (1–2)	1 (1–2)	0.21
CCI score	5 (4–5)	4 (4–6)$^{\Sigma}$	5 (4–5)	0.68
Comorbid conditions[b]	47 (51)	17 (49)	30 (52)	0.77
DM end organ complications	4 (4)	2 (6)	2 (3)	0.63
DM without end organ complications	12 (13)	6 (17)	6 (10)	0.34
Localized cancer ≤5y	5 (5)	1 (3)	4 (7)	0.65
Metastatic cancer ≤5y	3 (3)	1 (3)	2 (3)	1
Moderate to severe CKD	5 (5)	2 (6)	3 (5)	1
CHF	17 (18)	4 (11)	13 (22)	0.27
MI history	17 (18)	12 (34)	5 (9)	0.002
PVD	9 (10)	5 (14)	4 (7)	0.29
CVA and/or TIA	8 (9)	5 (14)	3 (5)	0.25
Dementia	3 (3)	2 (6)	1 (2)	0.55
CTD	3 (3)	1 (3)	2 (3)	1
Multiple myeloma	1 (1)	0 (0)	1 (2)	1
Number of GSF criteria	3 (1–4)	4 (3–5)	1 (0–3)	<0.001
Number of patients receiving PC	10 (10)	8 (23)	2 (3)	0.005

SQ+: "not surprised" as answer to SQ; SQ-: "surprised" as answer to SQ; COPD: chronic obstructive pulmonary disease; GOLD: global initiative for chronic obstructive lung disease; FEV_1: forced expiratory volume in 1 s; AECOPD: acute exacerbation COPD; HA: hospital admissions; CCI: Charlson comorbidity index; DM: diabetes mellitus; CKD: chronic kidney disease; CHF: congestive heart failure; MI: myocardial infarction; PVD: peripheral vascular disease; CVA: cerebrovascular accident; TIA: transient ischemic attack; CTD: connective tissue disease; GSF: gold standards framework; CI: confidence interval.

[a] *Values for categorical variables are given as count (percentage); for continuous, normally distributed, variables as mean (95% CI), for continuous, non-normally distributed, variables$^{\Sigma}$ and for ordinal variables as median (interquartile range).*

[b] *Comorbidity conditions based on Charlson comorbidity index.*

Sensitivity, specificity, and positive and negative predictive values

The SQ had a high specificity and very high positive predictive value (PPV, both 100%), with low sensitivity and negative predictive value (NPV, 44.9% and 25.9%, respectively) explained by a high rate of false negatives (Table 2.3). Results were the same when comorbidity was scored positive if patients had ≥2 comorbidities, instead of ≥1 comorbidity. In a stricter analysis, a cutoff point of ≥2 GSF criteria was used. False positive answers to the SQ raised from 0 to 4, resulting in a slightly lower specificity and PPV (88.2%, confidence interval (CI): 71.6-96.2 and 88.6%, CI: 72.3–96.3, respectively). Due to a higher amount of true negatives, sensitivity and NPV- improved, although they remained low (52.5%, CI: 39.2- 65.5 and 51.7%, CI: 38.3–64.9, respectively, Table 2.4).

Table 2.3 Sensitivity, specificity, positive predictive values, and negative predictive values of SQ versus ≥1 GSF indicator guidance

Surprise question	GSF+	GSF−	Total
SQ+	35	0	35
SQ−	43	15	58
Total	78	15	93
Sensitivity (%) and 95% CI	44.9 (33.7–56.5)		
Specificity (%) and 95% CI	100 (78.2–100)		
Positive predictive value (%) and 95% CI	100 (87.7–100)		
Negative predictive value (%) and 95% CI	25.9 (22.2–29.9)		

GSF: gold standards framework; SQ: surprise question; SQ+: "not surprised" s answer to SQ; SQ-:"surprised" as answer to SQ
CI: confidence interval.

Table 2.4 Sensitivity, specificity, positive predictive values, and negative predictive values of SQ versus ≥2. Criteria of GSF prognostic indicator guidance.

Surprise question	GSF+	GSF−	Total
SQ+	31	4	35
SQ−	28	30	58
Total	59	34	93
Sensitivity (%) and 95% CI	52.5 (39.2–65.5)		
Specificity (%) and 95% CI	88.2 (71.6–96.2)		
Positive predictive value (%) and 95% CI	88.6 (72.3–96.3)		
Negative predictive value (%) and 95% CI	51.7 (38.3–64.9)		

GSF: gold standards framework; SQ: surprise question; SQ+: "not surprised" as answer to SQ; SQ-: "surprised" as answer to SQ; CI: confidence interval.

DISCUSSION

This study showed that all patients identified as eligible for palliative care by the use of the HSQ would also have been identified as such by the GSF prognostic indicator guidance. In other words, a positive answer to the HSQ includes nearly half of the patients that could benefit from palliative care according to the GSF prognostic indicator guidance, with no false positives. Therefore, we demonstrated that the SQ in this population, with a recent hospitalization for COPD, can be used as a simple screening tool to identify patients in need of palliative care.

Few studies focusing on the SQ have been performed,most of them in cancer patients or in patients with advanced chronic conditions in general.[15,18,26-30] To the best of authors' knowledge, there are only two studies concerning COPD and the SQ,[31,32] one of which compared nonvalidated prognostic indicators and the answer to the SQ.[32] Their findings are consistent with our findings, with 87% meeting at least one prognostic indicator and a PPV of a "No" answer to the SQ of 95%. A recent study in patients with diverse chronic conditions[15] compared the predictive validity of the SQ and the NECPAL tool, a content-validated tool developed by their group. In contrast to our study findings, they found that 93% of SQ+ patients were also NECPALþ patients. However, criteria of the NECPAL tool differ from the GSF prognostic indicator guidance and need further modification. Reliability was also not tested in both of our studies, and a high inter- and intra-rater variability could be an explanation for the difference in results.
Although use of the SQ has been promoted by some,[29,33] others have highlighted concern about the implementation of the SQ into routine practice. Studies have reported confusion and discomfort among physicians using the SQ, as they preferred a more objective clinical terminology[34] and felt the SQ was too subjective to base important decisions on.[35] It must be emphasized that provision of palliative care should be based on

unmet end-of-life care needs,rather than on prognostication or a well-defined timescale. The SQ simply asks clinicians whether he or she thinks the patient "is sick enough to die" and could therefore benefit from palliative care. Accordingly, the SQ has been mentioned as a general indicator of unmet needs and physical decline.[36] This is supported by the results of our study, since all patients assessed as "not surprised" by the SQ also fulfilled at least one indicator of a tool that is developed to identify patients who may have these unmet needs or show physical decline. Moreover, a recent study to the provision of PC for COPD showed that from a large primary care cohort, only 7.8% received PC during their study follow-up.37 Our study group considered patients with more severe COPD (average FEV_1 of 45%), of whom only 12% received palliative care at the time of inclusion. One of the barriers for referral to PC in COPD is the complexity of tools to identify eligible patients.[38] Therefore, simple instruments to raise the amount of referrals are required. Our study showed that the SQ combined with recent hospitalization may provide an easily applicable method to rise outpatient palliative care referrals.

Strengths and limitations

This study is based on everyday clinical practice and the outcome is easily applicable for physicians. A limitation of this study is the fact that only COPD patients with a recent hospitalization have been included. Clinical parameters as well as the answer to the SQ may differ in patients who have not been hospitalized before, who suffer from other conditions than COPD, or when assessment takes place in a different setting (e.g. in primary care). Therefore, this study only provides information about patients with COPD who have been admitted to the hospital in the past 18 months.

Implications for further research

Since little is known about the efficacy of palliative care services in COPD,39 further research is needed to determine patients' and family outcomes after outpatient referral. Moreover, follow-up after referral is needed to determine if patients identified through the HSQ, experience a better quality of life after referral to a palliative care team. Further enhancement toward a comprehensive and integrated pathway for both inpatient and outpatient palliative care services is important. Finally, due to our study design with short follow-up time, we were unable to obtain mortality rates and correlate them to the answer to the SQ. This could be assessed in further research. However, the aim of this study was to investigate whether the SQ combined with hospitalization could provide an appropriate "short cut" for identifying patients in need of palliative care, rather than estimating prognosis.

CONCLUSION

In a subset of recently hospitalized COPD patients, the SQ presents high specificity and a high positive predictive value compared to the Gold Standard Framework Indicator Guidance and provides a quick and simple tool for identifying COPD patients who are likely to benefit from a palliative care approach. Due to a low sensitivity and a low negative predictive value, it should not be used as a stand-alone tool.

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Appendix 2.1

Questionnaire COPD and palliative care

1 Have you experienced shortness of breath in the past week?
If yes, which of the answers as stated below best describes your situation? (MRC dyspnoea scale)

- ☐ do not experience any breathlessness.
- ☐ Breathless only with strenuous exercise.
- ☐ Short of breath when hurrying on the level or up a slight hill.
- ☐ Slower than most people of the same age on a level surface or have to stop when walking at my own pace on the level.
- ☐ Stop for breath walking 100 m or after a walking few minutes at my own pace on the level.
- ☐ Too breathless to leave the house.

2. To which amount are you able to carry out activities? *(WHO performance scale)*

- ☐ Able to carry out all normal activity without restrictions.
- ☐ Restricted in physically strenuous activity but ambulatory and able to carry out light work.
- ☐ Ambulatory and capable of all self-care but unable to carry out any work; up and more than 50% of waking hours.
- ☐ Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
- ☐ Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

3. Have you lost more than 10% of your weight in the past 6 months?

- ☐ YES
- ☐ NO

4 Have you experienced any unexpected occurrence in your life, involving death or serious physical or psychological injury, or the risk thereof?

- ☐ YES
- ☐ NO

5 Do you believe you or you caregivers are in need of more care and/or support in your current situation?

- ☐ YES
- ☐ NO

translated from Dutch to English by one of the authors, Noppe

Part 2

On smoking-related stigma and patient perspectives on home oxygen therapy

Part 2

"This is what lies ahead."

Perspectives of oxygen-naïve COPD patients on long-term oxygen use. A qualitative study

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ABSTRACT

Purpose

Oxygen is commonly prescribed to patients with severe COPD. However, little is known about the perspectives COPD patients, who do not yet use oxygen, have on this treatment.

Patients and methods

A total of 14 oxygen-naïve patients with COPD Gold stages 3-4 and a high symptom burden participated in semi-structured interviews, in which their beliefs and expectations regarding oxygen therapy were explored. We used conventional content analysis to process our qualitative data.

Results

Four main themes were identified: seeking information, expected impact on quality of life, expected social impact and stigma, and last phase of life.

Conclusion

The message that home oxygen should be started, was regarded as bad news by most participants. The rationale behind the therapy and the way it is delivered were unknown to most participants. Some participants anticipated smoking-related stigma and social isolation. Misconceptions such as tank explosions, becoming housebound, full dependency on oxygen and an imminent death were common amongst interviewees. Clinicians should be aware of these fears and assumptions when communicating with patients on this subject.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent, life-threatening lung disease. Due to its chronic course and its huge impact on quality of life, COPD is a major cause of morbidity and health care utilization.[1] Disease progression often leads to hypoxemia, rendering a significant proportion of patients eligible for long-term oxygen therapy (LTOT).[2,3]

LTOT has been shown to increase survival in patients with COPD and severe hypoxemia,[4,5] for whom its prescription has since been recommended by international guidelines.[6,7] Moreover, in some studies on LTOT in hypoxemic COPD patients, exercise capacity and breathlessness improved and hospitalizations were reduced.[8,9]

Despite these potential beneficial effects, patients with LTOT may experience major physical and psychosocial disadvantages. A recent systematic review on studies reporting perspectives of patients with advanced illnesses on LTOT for reducing breathlessness, identified numerous burdens.[10] The handling of the equipment was cumbersome and hindered daily activities for some patients. Also, using LTOT led to significant emotional and psychological stress. Patients reported social isolation, safety concerns and an increased sense of vulnerability.
Understanding barriers, beliefs and expectations that patients may have when they hear that they are eligible for LTOT, is essential in providing adequate support and improving adherence. However, very little is known on the views and expectations of oxygen-naïve COPD patients. One qualitative study on perspectives of people experiencing breathlessness included six oxygen-naïve patients with various underlying conditions including COPD.[11] In this study, the important theme of anticipated stigma arose, as LTOT would make the illness visible. To our knowledge, all other studies on the psychosocial impact of LTOT included only oxygen users.[10,12-15] However, oxygen-naïve patients (defined as patients who have never been prescribed LTOT) are unlikely to have been adequately informed about LTOT and have not perceived its effects in their home environment. Therefore, they may have different assumptions than oxygen users. Awareness of these potential assumptions is helpful for healthcare professionals in order to effectively communicate with patients on LTOT. Therefore, the aim of this qualitative study is to explore the perspectives of oxygen-naïve COPD patients on LTOT who may need this therapy in the future.

MATERIAL AND METHODS

Study design

Since literature on the subject is limited, a qualitative descriptive study design was used, with in-depth, semi-structured interviews. The qualitative approach of interpretive description was used to capture themes and patterns within the perspectives of oxygen-naïve COPD patients about LTOT.[16] For analysis of the interviews, we chose to use inductive content analysis. This gave us the ability to gain insights into unique participant perspectives instead of using perceived categories.
The Medical Ethics Review Committee of the Amsterdam University Medical Centre concluded that this study was not subject to the Medical Research Involving Human Subjects Act.

Participants

We chose to recruit oxygen-naïve patients with COPD Gold stages 3-4 and a high symptom burden (≥ 2 exacerbations yearly and/or modified Medical Research Council (mMRC) 17 score ≥ 2), since they are most likely to be eligible for LTOT in the future. Consequently, these are the patients who are likely to have thoughts and expectations on this subject. Patients were recruited at the outpatient clinic of a large teaching hospital in an urban area in the Netherlands between November 2021 and May 2022. We purposefully sampled to recruit men and women with different ages, educational levels and smoking status. Exclusion criteria for participation were earlier use of LTOT and inability to participate (language barrier, cognitive impairment). Prior to each interview, written informed consent was obtained from each participant. Characteristics (age, gender, forced expiratory volume in one second (FEV_1), smoking status and mMRC score) were collected at the time of the interview, and the most recent spirometry was used.

Interviews

A semi-structured interview schedule was developed from the existing literature on COPD patients' experiences on LTOT. The topics included perceived effect of LTOT on self-image, on daily life, on social life, on mobility, and whether LTOT provoked shame (Table S3.1). We estimated a sample of about 15 interviews would be needed until data saturation was reached.
Three researchers (KM, ED and EM), carried out the interviews at locations chosen by the patients. There was a doctor-patient relationship between KM and the participants, and no relationship between the participants and the other two interviewers. Each interview took approximately 60 minutes, were audio-recorded and transcribed verbatim.

Data analysis

The first four interview transcripts were read by three researchers (KM, ED and EM) and coded line by line. Afterwards, codes were compared and discussed until consensus was reached. Since coding between all three researchers was comparable, the remaining interviews were coded by one researcher (KM). The coding process was performed using Atlas.ti Scientific Software v.8 (http://atlasti.com; Atlas.ti Scientific Software Development GmbH, Berlin, Germany). When coding was complete, the codes were grouped into themes by KM. Finally, codes and themes were discussed with the other three researchers (EM, ED, YE) until agreement was reached.

RESULTS

Fourteen patients were invited to participate (see table 3.1). All agreed to participate, gave informed consent and were interviewed. Of note, one of the participants (P14) was mistakenly included despite having COPD GOLD 2. Since we deemed her interview valuable, she was not excluded.
During the analysis process, it was identified after fourteen interviews that themes were saturated and therefore no further participants were sought.

From the narratives, four themes were distilled: (1) seeking information, (2) expected impact on quality of life, (3) social impact and stigma, and (4) last phase of COPD.

Table 3.1 characteristics of the participants

Characteristic		N (%)
Age	55-59	1 (7%)
	60-64	2 (14%)
	65-69	4 (29%)
	70-74	4 (29%)
	75-79	1 (7%)
	80-84	2 (14%)
Gender	Female	8 (57%)
	Male	6 (43%)
FEV1, % of predicted	25-29%	4 (29%)
	30-34%	2 (14%)
	35-39%	2 (14%)
	40-44%	3 (21%)
	45-50%	2 (14%)
	>50%	1 (7%)
Education *	Lower secondary	3 (21%)
	Upper secondary	8 (57%)
	Bachelor	3 (21%)
mMRC	2	5 (36%)
	3	6 (43%)
	4	3 (21%)
Smoking status	Former	9 (64%)
	Current	5 (36%)

**International Standard Classification of Education (ISCED) 2011*
FEV_1: forced expiratory volume in one second mMRC: modified Medical Research Council Dyspnea Scale

Theme 1: *Gathering knowledge*

We distinguished three patterns in patients' need for information. Some patients wanted all available information on LTOT. Several stated that it was essential to involve their family caregivers; one patient stated that a good relationship between healthcare provider and patient was likely to increase receptiveness for LTOT. A second group of patients was ambivalent in their need for information. On the one hand, there was a desire for information; on the other hand, they expressed a fear of confrontation. The desire for information would depend on the symptoms they experienced.

> ***"I am interested in my disease, what it does to other people and myself, and I try to find a certain balance. Let's say, at times when I am feeling not well, I am more interested in what the world has to offer for COPD, but that interest fades away once I am feeling better." (P10)***

A third group of patients stated that they'd rather bury their head in the sand, since the whole concept of LTOT was too distressing for them, although they acknowledged that they might have to change their attitude later.

''For someone with COPD, well let me speak for myself, sometimes there are things you just don't want to know about. It may sound strange, immature even, but I think I just don't want to know. I guess I'll see where the roads takes me." (P14)

When first asked on their views on LTOT, almost all patients responded with what they had seen in fellow patients. Seeing other patients with oxygen often had major impact; furthermore, patients often attempted to distill information from what they observed. This information was usually negative:

''I saw that man, he suffered from COPD as well, changing in four or five months from a normal person to … Well, he is three times as skinny as I am. That man is languishing. […] I don't see any positivity." (P11)

''I entered the physiotherapy clinic and saw a man coming in with an oxygen tank… I wanted to leave! This is what lies ahead. I was really shocked. And I thought, he can't even walk a bit on the treadmill. The whole time, I was completely fixated on that man." (P 12)

Theme 2: *Expected impact on quality of life*

The majority of patients expected oxygen to relieve their breathlessness. Some patients expected LTOT to increase their mobility, other patients thought it might be a relief during breathlessness crises.

''Walking distances, I think that's the only advantage. Just being able to walk longer distances, being able to go to the beach again." (P6)

''Just having a little boost sometimes, when being very out of breath." (P4)

As opposed to an increased life-space mobility, many patients expected that LTOT would make their world smaller. They mentioned several practical reasons: going outside would be complicated, the system would be heavy, or the battery would run out of power.

''You become fixated upon yourself, which can be tiresome. When using oxygen it shall be the same, continuously checking: 'Oh is there still enough', 'do I need to recharge it', 'are there parts that need to be replaced'." (P6)

''Now I am free to go wherever, but then I will be dependent on equipment I have to carry along." (P11)

Several patients mentioned being connected to a tube as a major drawback. This appeared to have two underlying assumptions. First, the notion that their mobility would be defined by the length of the tube. Second, the idea that they would be 'chained to something', not free.

Several patients pictured heavy metal tanks when they imagined what LTOT would be like. The idea of portable concentrators was far less threatening, but not all patients knew such portable systems existed. A possible reason, as stated by several patients, was that oxygen is 'invisible' on the streets.

''I've only seen people having an oxygen tank at home. None of them are leaving their houses anymore, their world shrinks. They let other people do things for them, although their car is parked right in front of their house. They don't come out anymore."(P11)

Besides portable concentrators, the idea of using LTOT 'on demand' was also far less threatening than using it continuously.

''I would not mind so much if I could use it shortly during the day. But when I hear about being connected to a tube for 16 hours, no that sounds awful to me." (P6)

When asked what would happen if the oxygen system would be near fire (e.g. from a cigarette), all participants stated that this would induce an explosion. This perceived explosion hazard led to feelings of anxiety in several participants.

Theme 3: *expected social impact and stigma*

Most patients expected that the start of LTOT would be a great shock to their loved ones. Some patients worried that their partner would turn into a caregiver. Furthermore, a negative impact on their own social life was expected by several patients. One reason mentioned was that the oxygen system would be too bothersome to take along. A second potential reason for patients was that they expected people to stop inviting them for outings if they were on LTOT. Several patients mentioned a third reason: they would be ashamed of the fact that they were dependent on oxygen, and consequently would see only their 'inner circle'. Some patients assumed that the use of LTOT would make them feel disregarded by society. They also used terms such as 'useless', 'a nobody', 'lamentable'. Linked to the shame is the feeling of guilt that some described. Apparently, they felt fully responsible for their illness and their need of LTOT.

''Well, now you've got it. They might say that. And rightly so. And they would say: you had it coming, my friend. Yeah, you're right, I'd say." (P8)

''But I think there is a certain barrier for your appearance, with people looking at you and thinking: 'wow, back off'. I don't know how to explain this, it is a certain kind of shame I guess." (P11)

''It triggers a lot of anger. I let this happen. I wish I hadn't - why did I start smoking?" (P12)

Theme 4: *Last phase of life*

Most patients assumed that prescription of LTOT would be triggered by a low level of functioning, not so much to correct hypoxemia. Most patients stated that LTOT was inevitable. Indeed, when they saw another patient on oxygen, they assumed it was their future too.
Several interviewees associated the start of LTOT with a shrinking world and with care dependency. For them, the prescription of LTOT would imply they had reached the terminal phase of their disease.

> ***''Mostly they crawl into their shells and stay in their houses in a very small circle. They build their whole world around them: a table, a seat or a sofa with a duvet on it, you know, that all turns into… Until it's over." (P11)***

> ***''It would scare me, because then you know you need a medical aid to stay alive. It is not just the idea of impairment, but also the feeling that you are reaching the end of life." (P10)***

> ***''For me, I think it would be the last phase of being ill but still being able to recover. I think when the oxygen comes, then that's over, that idea of recovering." (P11)***

Many believed the oxygen could not be switched off anymore, rendering them dependent on it. This alleged dependency triggered feelings of anxiety. Indeed, most patients stated that 'running out of oxygen' would make them very anxious. Also, it was common for patients to think that LTOT was addictive, and that the dosage would have to be increased in the future.

> ***''You start with one tablet, but at the moment I am taking around 12 of 13 tablets. It's the same with oxygen. You get used to it and then you become, you know, addicted.'' (P 4)***

DISCUSSION

Our findings describe important assumptions and beliefs that patients with severe COPD may have on LTOT. The finding that they may relate LTOT to the (literal) end of life, has not been described before. Consequently, the idea of being eligible for oxygen should be regarded as very distressing for a subset of patients with COPD.
Furthermore, LTOT provoked several emotions that clinicians should be aware of. Firstly, some patients anticipated that they would feel guilty. In their opinion, they should have prevented the need for LTOT through self-management. Feelings of guilt in COPD patients, due to self-inflicted disease associated with smoking habits, have been prescribed previously.[18,19] However, the fact that prescription of LTOT might be a trigger for self-blame has not been described before.
Secondly, interviewees anticipated stigma provoked bij LTOT. This finding is also in line with earlier studies.[10,11,14] In a qualitative study on how patients with severe COPD experience daily life, patients perceived social blame because society judges their diagnosis to be self-inflicted.[14] LTOT means the patient can no longer hide the disease, which may lead to anticipated stigma.[11] In the current study, several interviewees assumed they would become dependent on home care, would become housebound or would move to a nursing home. This complete disconnection from social life has been termed 'social death'.[20] Characteristics of social death are a loss of social identity, a loss of social connectedness and losses associated with disintegration of the body.
A third emotion that was expressed by several patients, was anxiety. This anxiety was triggered by several misconceptions. Patients believed that after LTOT, there would be no other options to prolong their life. Furthermore, it was common for patients to assume LTOT would mean their life depended on a machine. Some feared addiction. Another fear that was expressed by the participants in our study, and also in previous literature, was the fear of explosion.[21] Indeed, all patients in the current study stated that oxygen is an inflammable gas and a spark near the oxygen system would lead to an explosion. In reality, oxygen is not an inflammable gas, but makes other things ignite at a lower temperature. LTOT is associated with an increased risk of fire and burn injury, although the risk is probably very low in non-smokers.[22] Therefore, awareness of fire risk is essential, but a fear for explosion is unrealistic.

Our findings are useful for the clinician who wants to bring up the subject of LTOT. Although some patients want all available information, others want to avoid the subject. Of note, the desire for information can be subject to change, depending on actual symptoms. When preparing a conversation about LTOT, health care professionals should verify if, and to which extent, a patient wants to be informed at that moment. A useful way to do this the 'ask-tell-ask – method' in which one first asks permission to share information.[23] After giving part of the information, one asks how the patient feels after receiving it, before more information is given. If the patient reacts strongly to the concept of LTOT, the clinician should explore which emotions or assumptions are at play. An example of a useful sentence in this context is: "Some patients with COPD are ashamed to be seen with oxygen. How is that for you?" According to our findings, it is helpful to ask patients if they know other patients on LTOT, and if so, how it affected them. Indeed, in our study most participants based their views on LTOT on what they had seen in fellow patients. This was also found by Wrench, who interviewed patients after initiation of LTOT and described how memories of others on oxygen formed a source of anxiety.[15]
Our data indicate that the start of LTOT affects thoughts patients have on their future. This underscores the notion that starting LTOT is an appropriate moment for advance care planning, as has been suggested previously.[24] The timing of advance care planning in COPD may be challenging, partly because patients may regard their disease as a 'way of life'.[25] However, starting LTOT is a clear transition point within the disease trajectory that resonates with patients, and should serve as a 'flag' for clinicians to consider tasks of palliative care such as advance care planning.
Another relevant finding of our study is the lack of knowledge on the purpose of LTOT. All participants believed that either breathlessness or low levels of functioning were the reason for healthcare providers to prescribe LTOT. The primary goal of the therapy, correcting hypoxemia in order to prolong life, was unclear to patients. This is in line with previous research that showed low levels of factual knowledge about oxygen use and

a tendency to over-estimate potential benefits among patients with COPD.[26] Actively addressing misconceptions on the goal and effect of this therapy is important, since a lack of perceived benefit of LTOT is associated with non-adherence.[27]

Not all participants expected LTOT to improve their levels of functioning. On the contrary, several feared that LTOT would limit their activities, even shrinking their world. This finding is in line with the meta-analysis by Kochovska et al., who found that active patients felt limited by LTOT, while patients with severe breathlessness felt greater freedom after initiating oxygen therapy.[11] Of note, most participants lacked knowledge on different forms of portable oxygen systems, which partly explains their fear of becoming housebound. When informing patients on LTOT, it is advisable to show a (picture of a) portable oxygen system, so their fear of being connected to a heavy tank may be taken away.

Strengths and limitations.

To our knowledge, this is the first study that focusses entirely on the perspectives of oxygen-naïve COPD patients on LTOT. Interviewing these patients has yielded new insights that had not become obvious from studies on oxygen users. The results may be easily implemented in communication training for health care providers who prescribe LTOT.

Our study has some limitations. One patient with COPD GOLD 2 has been included, despite our inclusion criterium of an FEV_1 below 50%. Furthermore, the patients recruited for this study had a doctor-patient relationship with one of the researchers. This may have introduced a selection bias, with invited participants having stronger emotions about LTOT than the general population.

CONCLUSION

This study provides new insights in important topics that should be addressed during conversations on LTOT. First of all, clinicians should be aware of the possibility that they deliver bad news to patients. The rationale behind the therapy and the fact that it may be given with a portable system should be made clear. The clinician should assess whether patient and carer fear (smoking-related) stigma and social isolation. Misconceptions such as tank explosions, becoming housebound, full dependency on oxygen and an imminent death should be addressed. The initiation of LTOT presents a natural moment for advance care planning, because of the huge impact it may have on patients and carers.

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SUPPLEMENTARY MATERIAL

Table S3.1 Topic list

Topics	Questions (examples)
Perceived effect of LTOT	What are your thoughts on LTOT? What would it do to your body?
Daily life	How do you think your daily life would change with LTOT? What are the positive and negative aspects? What are your thoughts on having oxygen within your house? How do you think LTOT would affect your mobility?
Self-image	If you were on LTOT, would you feel different about yourself?
Social life	How do you think your loved ones would react if you started LTOT? Do you think you might be able to go on a holiday with LTOT?
Sexuality	If you were on LTOT, would you feel less attractive? Would it change the way you are intimate with your partner?
Shame	Some patients would feel ashamed to be seen with LTOT. Do you think you would experience that?
Fire hazard	If you used the LTOT and you would light a cigarette or would be near a flame, what do you think would happen?

Chapter 4a

Part 2

The Attitudes of Pulmonologists Regarding Smoking Behavior of Their Patients with Advanced COPD: A Qualitative Research

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic respiratory diseases. It affects about 3% of the population worldwide and is responsible for over 3 million deaths annually.[1] The burden of disease is high, due to the increasing prevalence and progressive disease course, which is characterized by exacerbations.[1,2] The WHO predicts that COPD will be the third leading cause of death worldwide in 2030.[3]

Cigarette smoking is the most important risk factor of COPD. The lifetime risk for smokers of getting COPD is estimated to be over 20%.[4] Cessation of smoking is beneficial since it improves survival in patients with COPD and improves the quality of life by many positive physiological and psychological effects.[4-6] However, smoking tobacco is extremely addictive,[7] and the use of tobacco is strongly influenced by industry marketing.[8] Tobacco marketing targets youth, seducing millions of teenagers to experiment with tobacco.[8-10]

Patients with diseases linked to smoking, including COPD, frequently perceive a health-related stigma.[11-15] In patients with COPD, the stigma on their smoking behavior has a strong emotional impact, regardless of their smoking status.[12] A large part of the population regards smoking as a choice instead of an addiction. Consequently, having COPD is seen as a personal responsibility.[11,16] This blaming attitude makes patients feel stigmatized, which causes feelings of guilt and shame.[11,13] Many patients experience little sympathy because COPD is regarded as a self-inflicted disease.[17] This may lead to isolation, loss of self-esteem, feelings of uselessness and even depression and anxiety.[11,14,18]

The sense of stigma and self-blame of patients with COPD can be reinforced by attitudes of health-care professionals.[14] Perceptions about the role of smoking in COPD differ between physicians and patients, with physicians seeing smoking as the leading cause of most cases of COPD, whilst patients often have different views.[19] Some patients with COPD believe that health-care professionals are biased against them because of their tobacco addiction.[20] This may lead to patients not being completely frank to their physician, a delay in seeking care, and even a decrease in medication adherence.[20,21]

Most studies performed on this topic have focused on patients' perspectives. One study used focus groups to explore the experiences of smokers with COPD and of physicians on smoking cessation in COPD. This study addressed three themes that hindered cessation: frustration in physicians, negative beliefs and lack of knowledge regarding cessation treatment, and health-care organizational factors.[22] Another study, using narrative medicine, found that pulmonologists often described their doctor–patient relationship as difficult, in cases where the patient continued to smoke.[23]

The aim of the current study was to explore the attitudes and behavior of pulmonologists in the Netherlands regarding the smoking behavior of patients with COPD.

MATERIALS AND METHODS

Study Design

To explore attitudes of pulmonologists regarding the smoking behavior of their patients with COPD, a qualitative design was used with in-depth semi-structured interviews. In the Netherlands, no medical ethical permission is required for interviewing health-care professionals, unless it concerns sensitive topics.

To guide the interviews, a topic list was developed. The initial topic list was constructed using knowledge from the existing literature on attitudes of professional caregivers regarding smoking-related behavior and stigma, and discussions between authors KM, YE- and KP, who have specific knowledge on palliative care, spiritual health care and smoking addiction in COPD. These main topics were[1] attitudes regarding smoking in general and [2] attitudes regarding smoking behavior of patients with COPD (See Appendix). If new topics emerged based on the obtained information from the first interviews, they were added to the topic list. All interviews were conducted by one researcher (GvdL), who had not met the interviewees before. Each face-to-face interview took approximately half an hour and was conducted in the hospital where the participating pulmonologist practiced. Openended key questions were used. After no new concepts were found, three additional interviews were performed to guarantee data saturation. For this reason, the sample size was not predetermined.

Participants

Pulmonologists, in most cases being the primary caregiver of patients with COPD next to general practitioners, were interviewed. Pulmonologists who worked in the three hospitals chosen for this study received an email with the invitation to participate. In two hospitals, pulmonologists work in partnerships and are therefore not employed by the hospital. In the third (academic) hospital, permission to contact the pulmonologists was obtained by the head of the department. Interviewees were registered pulmonologists in the Netherlands and not specialized in palliative care or smoking cessation. Purposive sampling was done to include both male and female pulmonologists, having different lengths of working experience, and working in different hospitals. Prior to each interview initiation, informed consent was obtained from the participants; consent to be in the study and for anonymous quotes to be used was given.

Data Analysis

The interviews were audio-recorded and transcribed verbatim. The transcripts were returned to the participants for comments or corrections. Three researchers (a pulmonologist, KM, a medical student in the final year of his master GvdL, a professor in spiritual health care, YE) independently open coded the first five interviews line by line with direct contentanalysis and compared and discussed the codes until consensus was reached on the code book. The remaining interviews were coded by one researcher (GvdL). During a meeting of two researchers (GvdL, YE), similar codes were merged. This coding process was performed using Atlas.ti software v.8 (http://atlasti.com; Atlas.ti Scientific Software Development GmbH, Berlin, Germany). Next, two researchers (GvdL, YE) grouped the codes into themes and sub-themes to get an overview of all mentioned determinants.

RESULTS

A total of 18 pulmonologists were interviewed, of whom 12 were women (67%). The age of the participants was between 35 and 63 years and they had 1 to 27 years of working experience as a pulmonologist. The interviews were held in three different hospitals in the Netherlands: one academic hospital and two large teaching hospitals. Saturation was reached after 15 pulmonologists had been interviewed. The initial number of 99 codes could be merged into 20 codes. These could be grouped into six categories. Out of these categories, we identified three themes: (1) attitudes towards smoking in general, (2) interaction between patient and physician, and (3) attitudes towards smoking cessation.

Attitudes Towards Smoking in General

Public Health

Almost all pulmonologists thought of tobacco as something negative and most of them stated that smoking needs to be banished. The participants reported different strategies to reduce smoking in society, such as increasing taxes or more laws on prohibiting smoking. The majority thought that the government acts too little on prevention and should protect its citizens.

> ***Of course, there's a very double interest, so partially it is for the state budget: it produces a lot. If people massively quit smoking, they live longer, so the pensions do not check out as well. So, it is discouraged, but it should all be a little firmer.***

Several participants recommended a change in funding on prevention and cessation of smoking from health-care insurance companies, and to tackle the tobacco industry. Some pulmonologists said that physicians do not take enough responsibility in helping their patients to quit smoking.

Responsibility

Most of the interviewees said it is hard to name one single party that can be held responsible for the smoking problem. All interviewees said that people are not or not fullyresponsible for their smoking behavior.

> ***A part is the mechanism of addiction; people often started at young age, indoctrinated by advertisements or herd behavior. To what extent can you still blame them now?***

However, most of them saw smoking also as a free choice or held smokers at least partially responsible for it. Besides, almost all pulmonologists reported the tobacco industry or the government to be responsible. Half of the interviewees stated that society in general or the socialenvironment of smokers are responsible.

Interaction Between Patient and Physician

Feelings of Physicians

Regarding patients with COPD who keep smoking, participants reported experiencing different feelings. The majority reported feelings of powerlessness, although some of them said that they developed a feeling of acceptance over time. Most participants reported feelings of frustration regarding the continuation of smoking.

> ***What you can say is: you must not moan about your COPD if you continue to smoke. Then I will not moan about smoking and you will not moan about your complaints.***

However, an equal number of participants reported compassion with smoking patients with COPD. A minority of the interviewed pulmonologists experience pride towards patients who managed to quit smoking, and a few said that they have the same approach to smokers and non-smokers. Several participants stated that their own attitude towards the smoking behavior of their patients had become more understanding over time.

Role of Physicians

The majority of the participants stated that pulmonologists should always support patients with COPD, regardless of their smoking state. On the other side, more than half of the pulmonologists had doubts about the usefulness of treatment and a minority of the pulmonologists reported feeling useless as a physician when a patient with COPD continues to smoke.

> ***I admit someone on the ward with an exacerbation of COPD. I admit him on a Saturday. I am doing the rounds on a Sunday, the nurse comes: "yes, he is downstairs smoking a cigarette."Then I think: you know, if you can smoke a cigarette during an exacerbation, then you might as well go home.***

Patient Perspective

Almost all participants recognized shame and feelings of guilt in a part of their patients with COPD.

> ***"Yes doctor, I have to admit something to you." They use that a lot the word "to admit"; that says something about how they feel about it. As if they owe me accountability.***

Most participants make an effort to take these feelings away. A few participants stated that only a minority of the COPD patients experience guilt and shame. A small group of physicians also noticed that some patients suffer from the blaming society and their social environment. Half of the interviewees observe that, as a consequence of the experienced shame and guilt, patients are not completely honest to the pulmonologists about their smoking behavior.

Smoking Cessation

For smoking cessation guidance, almost all participants refer patients to the general practitioner or a specialized smoking cessation clinic. More than half of the participants said that it is practically impossible for pulmonologists to guide patients in smoking cessation themselves.

However, the majority reported they discuss smoking cessation in every contact with their patients with COPD. Most participants tend to discuss the disadvantages of continuing more than the benefits of quitting. They reported to avoid being too harsh in their approach in order to maintain the therapeutic relationship. Some participants reported they use a stricter approach towards patients on smoking cessation, for example, threatening with ending treatment in the hospital.

> ***I am a little stricter. For example: I admit a patient with an exacerbation of COPD to the hospital. The next day I hear the nurse say: "the patient is downstairs to smoke a cigarette". In that case I think: if you can go downstairs to smoke a cigarette, then you might as well go home.***

Nearly every participant stated that the patient has his or her own responsibility in smoking cessation; two participants called it a choice not to quit smoking. Several participants reported that it is useless for a health-care professional to put an effort into smoking cessation if a patient does not make an effort as well.

> ***If it's purely externalizing, if I can put it like this, that they say: "solve it doctor. I'm getting sicker, but too bad! And you have to give me something which makes me feel better." Then I try to make them aware that it does not work this way.***

Half of the participants acknowledged that quitting tobacco use is very difficult for the patient and a few participants recognized feelings of fear and frustration in patients, who want to quit smoking but do not succeed. Furthermore, the social environment of the patient was mentioned multiple times. Several interviewed pulmonologists reported they often see family and friends putting pressure on the patient to quit smoking, whilst a few reported the social environment to be the main reason patients cannot quit smoking.

> ***I always try to take away the blaming part. Often you see families pushing to quit smoking in terms of: "why you just don't quit?" You want to prevent that. You want support, not punishment for their behavior.***

DISCUSSION

We identified three major themes regarding their attitudes towards smoking: attitudes towards smoking in general, smoking cessation, and the interaction between patient and physician.

This study showed that all interviewed pulmonologists agreed that patients cannot be fully held responsible for their smoking behavior. This was mostly because smoking was (correctly) seen as a strong addiction.[24] At the same time, smoking was also regarded as a choice by the majority of the participants. In other words, the respondents had contradictory views: almost all of them stated that patients are not fully responsible, and, on the other hand, thought that patients have their own responsibility in smoking cessation.

Most participants did not hold one single stakeholder responsible. Besides the tobacco industry, the government, the social environment and society, in general, were mentioned to play a role in smoking addiction. Indeed, having friends who smoke, low parental support, pro-smoking attitudes and low socio-economic status have been shown to be important factors predicting the initiation of smoking.[25] Heritability of higher susceptibility to nicotine dependence was also mentioned.[26] When asking for the best strategy to stop smoking on societal level, most participants pointed out that the government acts too little on prevention. Regarding smoking cessation for the individual patient, most pulmonologists in our study refer patients to their general practitioner In the Netherlands, general practitioners use a guideline, containing effective interventions for smoking cessation.[27]

An interesting finding in our study is that almost every participant mentions smoking cessation during every contact with their patients, although they believe the advice is futile if the patient does not have the motivation to quit smoking. This belief, however, is not correct; randomized controlled trials showed that a brief advice from a physician to stop smoking increases the rate of quitting of all who receive it, whether or not they were motivated to quit.[30] The offer to support them appears to be more effective than just the advice to stop.[25,31] This suggests that pulmonologists do not realize that they can manage to empower the intrinsic motivation to quit in patients with only a minor intervention. The majority of the interviewed pulmonologists said they do not want to be too stricttowards their patients, as they want to maintain the therapeutic relationship. This confirms the findings of a previous study that found that smokers with COPD are open to receive help and support but do not want to be patronized.[32] Some patient-centered styles of counseling, like motivational interviewing, can be useful and will enhance the therapeutic relationship without patronizing.[33]

Regarding the doctor–patient relationship, most interviewed pulmonologists reported feelings of powerlessness, followed by frustration and compassion concerning the smoking behavior of their patients. This is in line with findings of previous studies on perceptions of patients with COPD on physicians' attitudes: some patients reported being ridiculed or criticized, while others felt fully accepted and supported by their physician.[14] In our study, taking care of patients who have no motivation to quit smoking, was most

frequently mentioned as a source for feelings of powerlessness and frustration. It appeared that physicians do not always understand this "lack of motivation", although several explanations have been described in the literature.[28] Smokers with COPD report that in their vision of life, smoking cessation is not a priority. They are less knowledgeable about the health consequences of smoking and have little faith in the efficacy of smoking cessation aids.[28,29] On the other hand, patients perceive a lack of empathy from doctors and state that advice on smoking would have a more encouraging effect if there was more empathy reflected in the communication.[28] Most patients with COPD experience stigmatization and a lack of support from their social network, society and health-care professionals, due to their (history of) smoking behavior.[11,12,14,15] The notion that compassion from the physician with the smoking COPD patient might well be a key element in maintaining a positive doctor-patient relationship, and perhaps even in motivating the patient to stop smoking, has previously been suggested by the study of Banfi et al.[23] When using a narrative tool, prompting professionals to reflect on their own emotions in treating COPD patients, they found that pulmonologists who were able to overcome their initial discomfort, and listen to the patient, were more likely to find a strategy to encourage the patient to end their dependence. In our study, almost all participants recognized feelings of blame and shame in their patients, but they did not always attempt to reduce such feelings. According to these findings, communication training for pulmonologists should comprise three key elements:

1 Awareness of the "knowledge gap" between physicians and patients on the effects of smoking cessation.
2 Recognition of feelings of shame and blame, and making an effort to reduce these feelings.
3 Compassion with the COPD patient, who experiences a high burden of disease, partially caused by a smoking addiction.

Strengths and Limitations

To our knowledge, this study is the first study that explored the attitudes of physicians towards smoking behavior in patients with COPD using one-on-one interviews. These insights are important since patients with COPD should experience compassion from their pulmonologist when smoking addiction is addressed, whilst the success rate of their attempts to quit smoking should be maximized.

Our study has some limitations. Possibly, the pulmonologists gave socially desirable answers to the interviewer, expressing themselves more mildly than they actually feel. For assessment of the generalizability of our findings, the local cultural influences and regulations on tobacco must be kept in mind. Furthermore, the interviews were held in a period in which the problem around smoking and the tobacco industry received ample attention in the Dutch media. This was caused by a lawsuit against the tobacco industry for adding additives to make cigarettes more addictive, in order to get existing smokers to keep smoking and to get starting smokers addicted to cigarettes more quickly.[34] This may have influenced the views of the participants. Lastly, we only interviewed pulmonologists; other health-care professionals involved in the care for patients with COPD such as general practitioners and nurses may have different attitudes.

CONCLUSION

We found that pulmonologists in the Netherlands have an ambivalent attitude on smoking behavior in their patients with COPD. Many pulmonologists consider smoking a free choice and hold patients responsible for cessation, whilst on the other hand acknowledge the addictive nature of tobaccosmoking. Pulmonologists who treat smoking COPD patients experience feelings of powerlessness and frustration, but also compassion. They recognize feelings of blame and shame in their patients but do not always act upon them.

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Chapter 4b

Part 2

Veroordeel de COPD-patiënt niet!

Medisch Contact 2020

Kris Mooren
Karin Pool

Oordelen over rookgedrag kan een wig tussen arts en patiënt drijven

Als je roken niet als een verslaving ziet, maar als een keuze, is het lastig om compassie te voelen voor een patiënt die zijn gezondheid in gevaar brengt. Toch is compassie essentieel voorgoede zorg. Dat laten twee longartsen aan de hand van een casus zien.

Een vrouw van 63 jaar wordt opnieuw verwezen naar de polikliniek Longziekten wegens een hoge ziektelast bij ernstige COPD. Drie jaar geleden was ze ook al op de polikliniek. Spirometrie liet toen al een belangrijke daling zien van de eensecondewaarde, oftewel het geforceerd expiratoir volume (FEV_1). Haar longarts besprak tijdens dat consult de noodzaak om te stoppen met roken.
Bij het huidige consult is de longfunctie opnieuw verslechterd, met een FEV_1 van tussen 30 en 40 procent. De vrouw vertelt dat ze door dyspneu vrijwel niet buiten komt. Ze heeft een droogpoederinhalatordie ze meer dan vijftien keer per etmaal gebruikt - aanzienlijk meer dan aanbevolen. Er is geen praktijkondersteuner, longverpleegkundige of ergotherapeut betrokken, ze heeft geen fysiotherapie. Ze vertelt dat ze last heeft van somberheid en angstig is voor de toekomst. Op de vraag waarom ze niet eerder hulp heeft gevraagd, zegt ze dat ze twijfelt of ze wel recht heeft op zorg. Bij het vorige consult is haar verteld dat ze moet stoppen met roken en dit lukt niet. Ze vindt dat ze haar klachten aan zichzelf te wijten heeft. Als ze naar een arts gaat met longklachten weet ze dat het roken opnieuw ter sprake zal komen; dit geeft gevoelens van schaamte en zelfverwijt.

In gevecht

Deze feiten over COPD staan vast:
1 roken is de belangrijkste oorzaak van COPD;
2 bij COPD is stoppen met roken de meest effectieve interventie;
3 het is onze plicht om het belang van de rookstop met onze patiënten te bespreken.

Voor ons als hulpverleners is de oorzaak-gevolgrelatie helder, ook al is die niet een-op-een: niet alle rokers worden aangedaan en niet alle mensen met COPD rookten.

Veel rokende patiënten zijn dagelijks in gevecht met zichzelf

Het rookgedrag van patiënten wordt in onze overdracht prominent genoemd, het is een van de eerste vragen die we aan patiënten stellen.
En deze feiten over rookverslaving staan vast:
1 de meeste rokers raken verslaafd op de kinderleeftijd en daar zijn slechts enkele sigaretten voor nodig;
2 meer dan 80 procent van de rokers wil graag stoppen, maar slaagt er niet in;
3 de overheid onderneemt te weinig om haar burgers tegen rookverslaving te beschermen.

Veel rokende patiënten zijn dagelijks in gevecht met zichzelf. Zij voelen zich niet altijd gesteund door hun omgeving. Ze schamen zich dat ze COPD hebben en mogelijk draagt deze schaamte bij aan het feit dat COPD - wereldwijd doodsoorzaak nummer drie - voor de maatschappij een relatief 'onzichtbare' ziekte is. Er zijn geen grootscheepse publieks acties om COPD tegen te gaan, integendeel: het blijft griezelig stil. Helaas leveren wij als hulpverleners soms onbedoeld een bijdrage aan het schuldgevoel van rokers. Dit kan gebeuren als we het gesprek over rookverslaving beginnen zonder te vragen of de patiënt daarvoor op dat moment openstaat en zonder het gesprek goed in te leiden.

Heb compassie

Wees u bewust van de kwetsbare positie waarin de patiënt in de spreekkamer zich bevindt. Vraag eerst, of de patiënt op dat moment het gesprek over roken wil aangaan - misschien heeft hij een heel andere hulpvraag. Als de patiënt het niet over het roken wil hebben, vraag dan of u er een volgende keer op mag terugkomen. Het helpt de patiënt (en uw behandelrelatie) als u benoemt dat de patiënt u niet nodig heeft om te horen hoe slecht roken is. De reden dat u het gesprek aangaat is dat u hem wilt helpen en steunen. Benoem actief dat u hem zo goed mogelijk zult begeleiden, ook als het niet lukt om te stoppen met roken. Als uw patiënt zichzelf verwijten maakt, zou u kunnen zeggen dat u die verwijten niet deelt; dat u wel de tabaksindustrie verwijt dat ze haar product extreem verslavend heeft gemaakt. U zult merken dat u door bovenstaande communicatie niet tegenover elkaar, maar naast elkaar komt te staan.
Wees u vervolgens bewust van uw eigen 'innerlijke ruimte'. Voor een niet-roker is de situatie waarin de roker zich bevindt, moeilijk voorstelbaar. Frustratie, onbegrip en machteloosheid liggen op de loer.
Hulpverleners kunnen het gevoel krijgen dat rokende COPD-patiënten hun pogingen om hen beter te maken, ondermijnen. Voor een kwalitatieve studie naar de opvattingen van longartsen over rookverslaafde patiënten, interviewden we onder anderen een longarts die zei: 'Als je kan roken tijdens een opname voor een exacerbatie, dan kun je net zo goed naar huis gaan.' Dergelijke opvattingen, hoe invoelbaar ook, drijven een wig tussen arts en patiënt. Bij COPD ontstaan vaak ook problemen op de niet-somatische domeinen - denk aan angst, depressie, isolement. Om deze te signaleren is een veilige en respectvolle arts-patiëntrelatie essentieel.
Maar het allerbelangrijkste is: heb compassie. Ernstige COPD is een vreselijke aandoening - ook zonder de gedachte dat je het aan jezelf te danken hebt.

Part 3

On opioids for breathlessness management in severe COPD

Chapter 5

Part 3

Attitudes toward opioids for refractory breathlessness in COPD among Dutch chest physicians

Chronic Respiratory Disease 2015

Daisy Janssen
Sander de Hosson
Eline bij de Vaate
Kris Mooren
Albert Baas

ABSTRACT

Dyspnea is the most frequently reported symptom of outpatients with advanced chronic obstructive pulmonary disease (COPD). Opioids are an effective treatment for dyspnea. Nevertheless, the prescription of opioids to patients with advanced COPD seems limited. The aims of this study are to explore the attitudes of Dutch chest physicians toward prescription of opioids for refractory dyspnea to outpatients with advanced COPD and to investigate the barriers experienced by chest physicians toward opioid prescription in these patients.

All chest physicians (n = 492) and residents in respiratory medicine (n = 158) in the Netherlands were invited by e-mail to complete an online survey. A total of 146 physicians (response rate 22.5%) completed the online survey. Fifty percent of the physicians reported to prescribe opioids for refractory dyspnea in 20% or less of their outpatients with advanced COPD and 18.5% reported never to prescribe opioids in these patients. The most frequently reported barriers toward prescription of opioids were resistance of the patient, fear of possible adverse effects, and fear of respiratory depression. To conclude, Dutch chest physicians and residents in respiratory medicine rarely prescribe opioids for refractory dyspnea to outpatients with advanced COPD. This reluctance is caused by perceived resistance of the patient and fear of adverse effects, including respiratory adverse effects.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, incurable, and often progressive disease and is nowadays the third leading cause of death.[1] In the last decade, the needs for palliative care for patients with COPD have been recognized.[2] Cornerstone of palliative care is optimal symptom management.[3] Symptom burden of patients with advanced COPD is at least comparable to symptom burden of patients with cancer.[4] Dyspnea is themost frequently reported symptom of patients with advanced COPD.[5] Dyspnea has significant impact on the patient as well as the family caregiver and is a major determinant of health status.[6,7]

Previous studies have shown that opioids can relieve dyspnea.[8-10] Therefore, international statements recommend the use of opioids to treat refractory dyspnea in patients with COPD.[2,11] Nevertheless, the prescription of opioids in patients with advanced COPD seems limited.[5] In fact, only one-fourth of the patients with COPD received opioids in their last 6 months of life, while half of the patients with lung cancer received opioids.[12] Moreover, while 94% of the clinically stable outpatients with advanced COPD reported moderate to severe dyspnea, only 2% used opioids, such as morphine.[5] Exploring the attitudes of chest physicians toward prescription of opioids to patients with advanced COPD is needed to understand why implementation of guidelines concerning the use of opioids for refractory dyspnea in daily practice is limited.

A recent qualitative study highlighted discrepancies between the positive experiences of patients with advanced COPD with opioids and the reluctance of physicians to prescribe opioids for refractory dyspnea.[13] In a qualitative study by Young and colleagues,[14] family physicians reported barriers, such as insufficient knowledge, lack of education, and lack of guidelines, toward prescription of opioids. To date, quantitative data concerning attitudes of chest physicians toward prescription of opioids to outpatients with advanced COPD and refractory dyspnea are lacking. Moreover, barriers toward prescription of opioids as experienced by chest physicians remain unexplored. Insight in attitudes as well as barriers toward opioid prescription are necessary to develop a plan for implementation of current palliative care guidelines.

Therefore, the aims of this cross-sectional observational study were to explore the attitudes of Dutch chest physicians and residents in respiratory medicine toward prescription of opioids for refractory dyspnea in outpatients with advanced COPD and investigate the barriers experienced by chest physicians and residents in respiratory medicine toward opioid prescription in these patients. A priori, we hypothesized that Dutch chest physicians and residents rarely prescribe opioids to outpatients with advanced COPD and refractory dyspnea.

METHODS

All chest physicians (n = 492) and residents in respiratory medicine (n = 158) in the Netherlands were invited by e-mail to complete an online anonymous survey in August 2012. The questionnaire included items regarding generic characteristics of the respondents (sex, age, religious background, level of education, palliative care education, and

work setting); questions about attitudes toward prescription of opioids to outpatients with severe to very severe COPD and refractory dyspnea (defined as severe dyspnea, despite optimal pharmacological and nonpharmacological treatment, including pulmonary rehabilitation and long-term oxygen therapy as indicated); preferred opioids; and barriers toward opioid prescription. Nine possible barriers were included. These were selected based on previous qualitative studies[13,14] and expertise of the developers of the questionnaire. The questionnaire was developed by the Dutch 'NVALT Taskforce Palliative care for patients with respiratory disease', consisting of experts in the field of respiratory medicine and palliative care.

Medical ethical approval was not necessary, because this online survey does not fall under the Medical Research Involving Human Subjects Act.

Statistics

Statistics were performed using IBM SPSS statistics 21.0. Categorical variables are described as frequencies, while continuous variables were tested for normality and are presented as mean and standard deviation. We used frequencies to evaluate prescription of opioids and perceived barriers to prescription of opioids. Perceived barriers were compared between physicians who prescribed opioids to ≤20% of their outpatients with COPD and physicians prescribing to 21% -100% of their patients using χ^2 tests.
A binary logistic regression model was developed to identify the determinants of opioid prescription attitude. Opioid prescription attitude (prescription to ≤20% of the patients vs. prescription to 21% -100% of the outpatients with advanced COPD and refractory dyspnea) was entered as dependent variable. Because there are no data available about possible determinants of attitudes toward opioid prescription, variables were only included in the model if they showed a possible relationship with opioid prescription attitude ($p \leq 0.20$) in univariate analyses. Therefore, characteristics of physicians (age, sex, religious background, oncology as subspecialty, work setting (academic hospital vs. general hospital or center for pulmonary rehabilitation), level of education (chest physician vs. chest physician in training), and palliative care education) were compared between participants who prescribed opioids in ≤20% of their patients with advanced COPD and refractory dyspnea and participants who prescribed opioids to 21%– 100% of their patients with advanced COPD and refractory dyspnea, using independent sample t-test or χ^2 tests, as appropriate. Religious background and level of education were not related to opioid prescription attitudes ($p > 0.20$) and were excluded from the logistic regression model. A priori, a two-sided level of significance was set at $p \leq 0.05$. 15

Table 5.1 Characteristics of physicians[a]

Characteristics	
Male	88 (60.3%)
Age (years)	43.6 (9.8)
Religious background	
Christianity	81 (55.5%)
Other	16 (11.0%)
None	49 (33.5%)
Level of education	
Chest physician	111 (76.0%)
Resident in respiratory medicine	35 (24.0%)
Palliative care education	86 (58.9%)
Main type of practice	
University hospital	33 (22.6%)
General hospital	108 (74.0%)
Pulmonary rehabilitation centre	5 (3.4%)
Subspecialty	
COPD	24 (16.4%)
Oncology	38 (26.1%)
Asthma	7 (4.8%)
Pulmonary rehabilitation	4 (2.7%)
Interstitial lung disease	6 (4.1%)
Respiratory infections	7 (4.8%)
None	60 (41.1%)

COPD: chronic obstructive pulmonary disease. an = 146.
Data are represented as number (%) or mean (SD).

RESULTS

Study participants

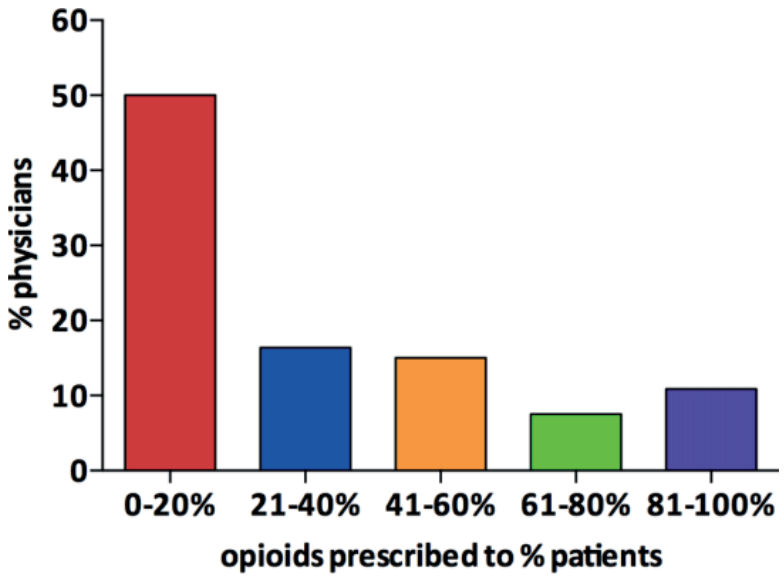
In total, 146 physicians (111 chest physicians and 35 residents in respiratory medicine) completed the online survey (response rate 22.5%; Table 5.1). Distribution of sex and proportion of residents among participants was representative for the total population of chest physicians and residents in respiratory medicine in the Netherlands (both, $p = 0.80$). However, participants more often worked in an academic hospital than the total population of chest physicians and residents in the Netherlands (22.6% vs. 15.3%, $p = 0.04$).

Attitudes toward prescription of opioids

Half of the respondents reported to prescribe opioids for refractory dyspnea in 20% or less of their outpatients with advanced COPD and 18.5% reported never to prescribe opioids for refractory dyspnea to these patients (Figure 5.1). Some differences were present between physicians who rarely or never prescribed opioids and physicians who more often prescribed opioids for dyspnea in COPD. Univariate analyses suggested a

relationship between attitudes toward opioid prescription and age, work setting, and oncology as subspecialty. Logistic regression analyses confirmed these findings. Physicians who prescribed opioids to 0%–20% of their patients with advanced COPD were older, more often worked in an academic hospital and less frequently reported oncology as subspecialty (Table 5.2).

Figure 5.1



Attitudes toward opioid prescription. Proportion of physicians prescribing opioids to 0% - 20%, 21% - 40%, 41% - 60%, 61% - 80%, and 81% -100% of their COPD outpatients with refractory dyspnea. COPD: chronic obstructive pulmonary disease.

Table 5.2 Determinants of prescribing opioids to 20% or less of the patients with advanced COPD and refractory dyspnea.[a]

	Prescribing to 0-20% (n = 73)	Prescribing to 21%–100% (n = 73)	Unadjusted *p* value	OR (95% CI)[b]
Age (years)	45.3 (10.7)	41.9 (8.5)	0.03	1.06 (1.01–1.11)
Male	48 (65.8%)	40 (54.8%)	0.18	1.39 (0.63–3.10)
Physician in academic hospital	23 (69.7%)	10 (30.3%)	0.01	3.80 (1.50–9.60)
Oncology as subspecialty	12 (31.6%)	26 (68.4%)	0.008	0.35 (0.14–0.84)
Palliative care education	38 (52.1%)	48 (65.8%)	0.09	0.57 (0.26–1.26)

[a]*Data presented as mean (SD) or number (%).*
[b]*Based on binary logistic regression analysis, R2 = 0.22.*

Table 5.3 Physician perceived barriers to prescription of opioids.[a]

	Total group (n = 146)	Prescribing to 0%–20% (n = 73)	Prescribing to 21%–100% (n = 73)	*p* Value
Possibility of respiratory depression	29 (19.9%)	15 (20.5%)	14 (19.2%)	1.00
Side effects such as nausea, constipation, or drowsiness	77 (52.7%)	33 (45.2%)	44 (60.3%)	0.10
Resistance patient	94 (64.4%)	38 (52.1%)	56 (76.7%)	0.003
Unpredictable which patients will respond to opioids	21 (14.4%)	16 (21.9%)	5 (6.8%)	0.02
Insufficient expertise to prescribe opioids	21 (14.4%)	18 (24.7%)	3 (4.1%)	0.001
Insufficient scientific evidence for beneficial effect on dyspnea among patients with advanced COPD	11 (7.5%)	9 (12.3%)	2 (2.7%)	0.06
Insufficient scientific knowledge concerning safety aspects	7 (4.8%)	7 (9.6%)	0 (0%)	0.02
Opioids are only indicated for terminal patients	2 (1.4%)	2 (2.7%)	0 (0%)	0.48
Possibility for development of physical or psychological dependence	10 (6.8	4 (5.5%)	6 (8.2%)	0.74

COPD: chronic obstructive pulmonary disease.
[a]*Data presented as number (%).*

Barriers towards prescription of opioids

The mean number of perceived barriers was 1.9 [1,2]. None or one barrier was reported by 39.7% of the respondents, while three or four barriers were reported by 24.0%. The most frequently reported barrier toward prescription of opioids for refractory dyspnea in patients with advanced COPD was resistance of the patient to receive opioids. Another important barrier was fear of possible adverse effects such as nausea, constipation, or drowsiness. The possibility of inducing respiratory depression was reported by 19.9% of the physicians as a barrier (Table 5.3). Five physicians reported barriers not included in the questionnaire, namely, risk of delirium (n = 3); preference for benzodiazepines for refractory dyspnea (n = 1), and polypharmacy (n = 1).

Differences were present between barriers perceived by physicians who rarely or never prescribed opioids compared to physicians who more frequently prescribed opioids to outpatients with COPD. Physicians who prescribed opioids to 0–20% of their outpatients with COPD less frequently reported the barrier ''resistance of the patient'' but more frequently reported ''it is unpredictable which patients will respond to opioids,'' ''I have insufficient expertise to prescribe opioids,'' and ''there is insufficient scientific knowledge concerning safety aspects'' (Table 5.3).

Preferred opioids

The most frequently prescribed long-acting opioids were orally administrated sustained release morphine and orally administrated sustained release oxycodone (Table 5.4). About one-third of the respondents always prescribed short-acting opioids for breakthrough dyspnea next to long-acting opioids. The most preferred short-acting opioid was oral morphine. Most respondents reported to prescribe laxatives next to opioids. Anti-emetics were prescribed by 5.5%of the physicians.

DISCUSSION

Key findings

In this cross-sectional observational study, we showed that half of the Dutch chest physicians or residents in respiratory medicine rarely or never prescribed opioids to outpatients with advanced COPD and refractory dyspnea. The most frequently reported barriers to prescription of opioids in this group were resistance of the patient, the physician's fear of adverse effects such as nausea, constipation, or sedation, and fear of respiratory depression.

Attitudes toward prescription of opioids

In this study, 50% of the physicians rarely or never prescribed opioids for refractory dyspnea to outpatients with advanced COPD. Moreover, 18.5% never prescribed opioids to these patients, despite the recommendations in national and international statements.[2,11,16] Our results confirm the findings of a previous Dutch study showing that opioids are rarely prescribed to outpatients with advanced COPD and severe dyspnea.[5] Reluctance toward prescription of opioids for dyspnea in COPD is also reported in other countries. Gaspar et al.[17] performed a survey about end-of-life care in COPD among 136 Portuguese chest physicians. They showed that 30% of the physicians never or rarely treated dyspnea in patients with COPD with opioids, while 38% reported to use opioids frequently or always to palliate dyspnea. The higher proportion of Portuguese physicians willing to prescribe opioids may be explained by the fact that we focused on prescription of opioids in outpatients with advanced COPD, while the study from Gasper et al.[17] focused on end-of-life care. A study among 65 hospital physicians in the United Kingdom showed recently that while most of them were willing to prescribe opioids for refractory dyspnea, only one-third had prescribed opioids to a patient with COPD. Moreover, they felt more confident in prescribing opioids to patients in the last days of life or patients with cancer than to patients with COPD.[18]

Barriers toward prescription of opioids

Surprisingly, the most frequently reported barrier by physicians was resistance of the patient to receive opioids. Conversely, Rocker et al.[13] reported positive experiences of patients with advanced COPD with opioids. In this qualitative study, patients reported that opioids provided them a sense of calm and relief from dyspnea and improved their quality of life. Moreover, family members reported that opioids were helpful for their loved ones and adverse effects were not a major concern. Another Canadian study also described COPD patients' positive experiences with opioids and showed that minor improvements in dyspnea may considerably improve the quality of life.[19] Further studies exploring the attitudes of patients with COPD toward the use of opioids is necessary to explain this discrepancy. Indeed, we don't know whether resistance toward opioids is common in patients with COPD or that it is only a perception of the chest physicians.

Fear of adverse effects was another important barrier. Indeed, the most common adverse effect of opioids is constipation.9 Therefore, almost all physicians in the current study

Table 5.4 Preferred opioids.[a]

	Number (%)
Preferred long-acting opioid	
Morphine sustained release (oral)	48 (32.9%)
Oxycodone sustained release (oral)	38 (26.0%)
Fentanyl (transdermal)	28 (19.2%)
Other[b] (oral)	5 (3.4%)
Never prescribe long-acting opioid	27 (18.5%)
Prescription of short-acting opioid for breakthrough dyspnea next to long-acting opioid	
Always	54 (37.0%)
As indicated	49 (33.5%)
Never	43 (29.5%)
Preferred short-acting opioid	
Morphine (oral)	73 (50.0%)
Oxycodone (oral)	33 (22.6%)
Fentanyl (transmucosal)	13 (8.9%)
Never prescribe short-acting opioid	27 (18.5%)
Prescription of laxatives and anti-emetics next to opioids	
None	10 (6.8%)
Laxatives only	128 (87.7%)
Anti-emetics only	0 (0%)
Laxatives and anti-emetics	8 (5.5%)

an = 146.
[b] Codeine, buprenorphine, or hydromorphone.

prescribed laxatives next to opioids. In the study by Abernethy et al.,[9] adverse effects (including nausea, vomiting, or sedation) of morphine prescribed for dyspnea were minimal.

Fear of respiratory depression is reported by one-fifth of the physicians as a barrier toward opioid prescription. The current literature about the safety of opioids for the treatment of severe dyspnea in patients with COPD is limited. Small studies in cancer patients showed no relevant respiratory adverse effects.[20 - 23] Abernethy et al.[9] found similar respiratory rates for 18 patients receiving morphine and 20 patients receiving placebo. However, they did not assess carbon dioxide levels. A randomized study in 14 COPD patients showed that 2.5-7.5 mg of diamorphine had no significant effect on blood gases.[24] Poole and colleagues found no change in oxygen saturation of 14 COPD patients during a 6-week treatment with sustained release morphine.25 On the other hand, the use of higher dosages of oral morphine during exercise testing caused higher carbon dioxide levels and lower oxygen levels in a study including 13 normocapnic patients with COPD.[26] Finally, a recent population-based prospective cohort study suggested

that lower dose opioids (≤30 mg oral morphine equivalents a day) were not associated with increased mortality, while a higher dose opioids was associated with increased mortality. However, respiratory adverse effects were not investigated in this study.[27] Therefore, further studies need to explore whether morphine leads to respiratory adverse effects in patients with COPD.

The difficulty in predicting which patients are likely to respond to opioids is another reported barrier, especially among physicians who never or rarely prescribed opioids. Indeed, in about one-third of the patients, opioids don't relieve dyspnea and to date it remains difficult to predict which patient is likely to respond.[10,28] A pooled analysis suggested that the likelihood of response is independent from the underlying disease. Patients with more severe dyspnea are more likely to respond to opioids.29 Other predictors of response are currently unknown. So, especially for patients with severe dyspnea, prescription of opioids, including careful monitoring of the benefits and adverse effects, can be considered.

Frequently reported barriers among family physicians toward prescription of opioids in COPD are insufficient knowledge and lack of education.[14] In the current study, insufficient expertise was reported more frequently by physicians who rarely prescribed opioids than by physicians who more frequently prescribed opioids. In contrast, palliative care education was not a significant predictor of opioid prescription behavior. This may be explained by the fact that weasked for education about palliative care in general and didn't ask specifically for education about palliative treatment of dyspnea in COPD.

Preferred opioids

Oral morphine is the preferred opioid for Dutch chest physicians. This can be explained by the fact that morphine is used in important studies in this field[9,10] and therefore is emphasized in the Dutch guideline about palliative treatment of dyspnea.[16] Fentanyl transdermal is the first-choice long-acting opioid for 19% of the physicians and fentanyl transmucosal the first-choice short-acting opioid for 9% of the physicians. This is surprising, because literature on the efficacy of fentanyl for treatment of dyspnea is scarce. While a few case studies suggest that fentanyl may be beneficial, two pilot randomized controlled trials were unable to show a difference between fentanyl and placebo.[30,31] Another trial including 12 patients with COPD suggested a positive effect of inhalation of fentanyl on exercise tolerance.32 An advantage of fentanyl may be the possibility for different administration routes. This can be especially important for treatment of breakthrough dyspnea. Only one-third of the respondents always prescribe short-acting opioids for breakthrough dyspnea next to long-acting opioids. Nevertheless, episodes of breakthrough dyspnea are hard to cope with for patients as well as their loved ones.[7] Patients prefer intranasal or sublingual administration routes above oral administration routes in episodic dyspnea.[33] Therefore, adequately powered randomized controlled trials should explore the effect on dyspnea, including episodic dyspnea, of different opioids and different administration routes.

Methodological considerations

Several limitations should be considered in interpreting the results. First, the response rate was only 22.5%. We don't know whether the attitudes toward opioids of participants in the survey are comparable with the attitudes of physicians who did not respond to our request. The proportion of the participants working in an academic setting was higher than in the total Dutch population of chest physicians and residents in respiratory medicine. Moreover, physicians working in an academic setting were less likely to prescribe opioids. Therefore, willingness to prescribe opioids could be higher among Dutch chest physicians and residents than in the current sample. Second, our survey assessed attitudes of physicians and does not provide objective data concerning actual opioid prescription behavior. However, attitudes are important to explore for the development of strategies for implementation of guidelines. Third, our regression model exploring determinants of attitudes only included a limited number of covariates. Therefore, other determinants of attitudes toward opioid prescription may be present which are not assessed in the current study. Finally, only 14% of the respondents reported insufficient expertise to prescribe opioids. We did not include an assessment of knowledge and skills concerning opioid prescription in COPD in our study. Therefore, the need for further education about opioids among chest physicians remains unexplored.

Conclusions and implications

Dutch chest physicians and residents in respiratory medicine rarely prescribe opioids for refractory dyspnea to outpatients with advanced COPD. This reluctance is caused by perceived resistance of the patient and fear of adverse effects, including respiratory adverse effects. In addition, predicting which patients are likely to respond to opioids remains difficult. To facilitate implementation of current guidelines about opioid prescription for dyspnea, these barriers need to be addressed. Therefore, future studies should explore the perceived resistance of patients, the occurrence of adverse (respiratory) effects of opioids in COPD, and how to select which patients are likely to respond to opioids. Guidelines about the use of opioids for dyspnea should include prevention and management of adverse effects. Finally, adequately powered randomized controlled trials are needed to explore the effect of different opioids and different administration routes on dyspnea, including episodic dyspnea.

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Part 3

Chapter 6

Opioids in patients with COPD and refractory dyspnea: literature review and design of a multicenter double-blind study of low dosed morphine and fentanyl (MoreForCOPD)

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ABSTRACT

Background

Refractory dyspnea or breathlessness is a common symptom in patients with advanced chronic obstructive pulmonary disease (COPD), with a high negative impact on quality of life (QoL). Low dosed opioids have been investigated for refractory dyspnea in COPD and other life-limiting conditions, and some positive effects were demonstrated. However, upon first assessment of the literature, the quality of evidence in COPD seemed low or inconclusive, and focused mainly on morphine which may have more side effects than other opioids such as fentanyl.

For the current publication we performed a systematic literature search. We searched for placebo-controlled randomized clinical trials investigating opioids for refractory dyspnea caused by COPD. We included trials reporting on dyspnea, health status and/or QoL. Three of fifteen trials demonstrated a significant positive effect of opioids on dyspnea. Only one of four trials reporting on QoL or health status, demonstrated a significant positive effect. Two-thirds of included trials investigated morphine. We found no placebo controlled RCT on transdermal fentanyl. Subsequently, we hypothesized that both fentanyl and morphine provide a greater reduction of dyspnea than placebo, and that fentanyl has less side effects than morphine.

Methods

We describe the design of a robust, multi-center, double blind, double-dummy, cross-over, randomized, placebo-controlled clinical trial with three study arms investigating transdermal fentanyl 12 mcg/h and morphine sustained- release 10 mg b.i.d. The primary endpoint is change in daily mean dyspnea sensation measured on a numeric rating scale. Secondary endpoints are change in daily worst dyspnea, QoL, anxiety, sleep quality, hypercapnia, side effects, patient preference, and continued opioid use. Sixty patients with severe stable COPD and refractory dyspnea (FEV_1 < 50%, mMRC ≥ 3, on optimal standard therapy) will be included.

Discussion

Evidence for opioids for refractory dyspnea in COPD is not as robust as usually appreciated. We designed a study comparing both the more commonly used opioid morphine, and transdermal fentanyl to placebo. The crossover design will help to get a better impression of patient preferences. We believe our study design to investigate both sustained-release morphine and transdermal fentanyl for refractory dyspnea will provide valuable information for better treatment of refractory dyspnea in COPD.

Background

Refractory dyspnea or breathlessness is a common symptom in patients with advanced chronic obstructive pulmonary disease (COPD), with a prevalence of up to 94% in the last year of life[1, 2]. It is defined as persisting complaints of dyspnea despite optimal standard therapy including, but not limited to smoking cessation, education, inhaled bronchodilators and pulmonary physiotherapy[3]. Refractory dyspnea is known to severely impact quality of life and exercise tolerance, and to increase the risk of depression and anxiety[4]. As the prevalence of COPD is expected to rise during the upcoming decades [5], it is likely that the number of patients with COPD suffering from refractory dyspnea will also continue to grow.

Advanced treatments such as non-invasive ventilation, bronchoscopic lung volume reduction and lung transplantation can improve dyspnea and quality of life in patients with advanced COPD[6]. But these treatments are only available for a proportion of patients with advanced COPD, due to strict eligibility criteria, high health-care costs and sometimes scarcity. Therefore, there is still a need for more widely available treatments of refractory dyspnea. In this context low dosed opioids have previously been investigated, and some positive effect was demonstrated [7-9]. However, whether the quality of the evidence is sufficient is still a topic of discussion. Furthermore, despite a positive advice on opioids in palliative care guidelines for COPD, prescriptionappears to be low in clinical practice[10-12].

We performed a systematic literature search with respect to opioids for refractory dyspnea in COPD, which we updated for the current publication to include all recent trials. We searched for placebo-controlled randomized clinical trials investigating any type of opioid prescribed for dyspnea reduction in COPD (at least 50% of participants).
We included trials reporting on dyspnea, health status and/or quality of life. Additional details on the search strategy can be found in the online supplement, including a flow chart on the number of records identified, screened and included.

Table 6.1 shows an overview of the trials we identified as a result of our search strategy. In total, fifteen trials were included. A statistically significant positive effect on dyspnea of opioid versus placebo was demonstrated only in three studies[7, 8, 13]. Since the majority of these studies included a small number of patients, the lack of statistically significant results may in part be explained bya low statistical power to detect a treatment effect. This assumption is supported by a meta-analysis published by Ekström et al. in 2015, in which a positive effect on dyspneawas found for both systemically administered and nebulized opioids (analyses of combined data of 8 and 4 trials, respectively)[14]. Nevertheless, the three largest studies in our table, which all have been published more recently, demonstrated no significant change in dyspnea for sustained-release morphine and oxycodone[15-17].
While assessing this, it is important to note that in the studies of Currow et al.[15] and Ferriera et al.[15] (which were originally both part of a three-armed trial) all arms received immediate-release morphine as needed. For both studies, the immediate-release morphine was used significantly more frequently in the placebo group (8.7 vs. 5.8 and 7.0

Table 6.1 Overview of randomized clinical trials investigating the effect of opioids on dyspnea, quality of life or health status in COPD

References	Design	n (% COPD)	Setting	Comparison	Treatment duration	Breathlessness			Quality of life or health status		
						Measurement (scale)	Opioid	Placebo	Measurement (scale)	Opioid	Placebo
Woodcock et al. [18]	Cross-over	12 (100)	Outpatient	Dihydrocodeine	Single dose	VAS (0–10 cm) 45 min after med	5.54 ± 1.91	6.33 ± 2.0	–	–	–
Light et al. [19]	Cross-over	13 (100)	Outpatient	Oral morphine 0.8 mg/kg	Single dose	Borg score (0–10) Rest	0.29 ± 0.58	0.13 ± 0.23	–	–	–
Jankelson et al. [20]	Cross-over	16 (100)	Outpatient	Nebulized morphine 20/40 mg	Single dose	Borg score (0–10) After 6MWT	4.2 ± 2.1/4.3 ± 1.8	4.3 ± 2.2	–	–	–
Noseda et al. [21]	Cross-over	14 (79)[#]	Hospitalized	Nebulized morphine 10/20 mg ± oxygen	Single dose	VAS (− 100 to + 100%)	+ 33 ± 28/+ 43 ± 27	+ 42 ± 27	–	–	–
Jensen et al. [22]	Cross-over	12 (100)	Outpatient	Nebulized fentanyl 50 µg	Single dose	Borg score (0–10) Isotime CPET	2.0 ± 0.5	2.6 ± 0.5	–	–	–
Abdallah et al. [13]	Cross-over	20 (100)	Outpatient	Morphine dose up to 10 mg	Single dose	Borg score (0–10) Isotime CPET	3.0 ± 1.6*	4.2 ± 2.6	–	–	–
Iupati et al. [23]	Cross-over Multicenter	21 (62)	Outpatient	Intranasal fentanyl 20 µg as needed	1 day	VAS (0–100 mm) 15 min after med	26 ± 21 (Δ29 ± 25)	21 ± 19 (Δ33 ± 24)	–	–	–
Abernethy et al. [7]	Cross-over Multicenter	48 (88)[#]	Outpatient	SR morphine 20 mg od	4 days	VAS (0–100 mm) Morning/evening	40.1 ± 24*/40.3 ± 23*	47.7 ± 26 49.9 ± 24	Data not presented	Data not presented	Data not presented
Janowiak et al. [24]	Cross-over	10 (100)	Hospitalized	Nebulized morphine 3–5 mg qid	4 days	VAS (0–100 mm) Now (2dd)	Δ25.4 ± 9.0[$]	Δ6.3 ± 7.8	–	–	–
Johnson et al. [8]	Cross-over	18 (100)	Outpatient	Dihydrocodeine 15 mg as needed up to tds	7 days	VAS (0–10 cm) Mean daily	4.6 ± 2.1*	5.6 ± 2.3	–	–	–
Currow et al. [15]	Parallel Multicenter	284 (58)[#]	Outpatient	SR morphine 20 mg qd All arms: morphine 2.5 mg as needed	7 days	VAS (0–100 mm) Now (2dd)	Δ-5.00 ± 2.13	Δ-4.86 ± 2.07	EORTC-QLQ-C15 PAL (0–100)	Δ1.8 ± 2.2	Δ1.5 ± 2.2
Ferriera et al. [16]	Parallel Multicenter	155 (60)[#]	Outpatient	Oxycodone 5 mg tds All arms: morphine 2.5 mg as needed	7 days	VAS (0–100 mm) Now	Δ-3.7 ± 2.9	Δ-9.0 ± 2.7	EORTC-QLQ-C15 PAL (0–100)	Δ-1.7 ± 3.1	Δ2.82 ± 3.1
Eiser et al. [25]	Cross-over	14 (100)	Outpatient	Diamorphine 2.5/5 mg qid	14 days	VAS (0–10 cm)	7.0 ± 0.7/7.0 ± 0.8	6.5 ± 0.7	–	–	–
Verberkt et al. [17]	Parallel Multicenter	124 (100)	Outpatient	SR morphine 10 mg 1-tds	28 days	NRS (0–10 points) Mean	Δ-0.60 (− 1.55 to 0.35)		CAT (0–40)	Δ-2.18 (− 4.14 to − 0.2)*	
Poole et al. [9]	Cross-over	16 (100)	Outpatient	SR morphine 10 mg od or bid	42 days	DBS (0–5)	2.22	2.26	CRQ (20–140)	Δ2.08 ± 4.53	Δ2.94 ± 3.46

Data presented as mean ±SD

od once a day, bid twice daily, tds three times a day,
qid four times a day, SR sustained release, VAS visual analogue score, DBS daytime breathlessness score, NRS numeric rating scale, CRQ chronic respiratory questionnaire, EORTC-QLQ-C15 PAL Quality of life questionnaire developed by the European Organisation for Research and Treatment of Cancer, CAT COPD assessment test, CPET cardiopulmonary exercise testing, 6MWT 6-min walking test
**p < 0.05 opioid versus placebo, [$]p < 0.05 change after treatment. [#]Data not exclusively on COPD*

vs. 4.2 daily doses, respectively)[15, 16] making an overall effect of the maintenance morphine moredifficult to detect. Furthermore, in the study by Verberkt et al. there was a statistically significant effect on worst daily dyspnea measured on a numeric rating scale (NRS) in a subgroup of COPD patients with a modified MedicalResearch Council (mMRC) ≥ 3 (mean difference comparedto placebo: − 1.33 (− 2.50 to − 0.16) points)[17].

Information on quality of life or health status was limited to four RCT's. Of these, only the study by Verberkt et al. demonstrated a small positive, statistically significant effect on health status measured with the COPD assessment test (CAT)[17]. Our search identified no placebo-controlled RCT's investigating transdermal fentanylfor refractory dyspnea in COPD.

Based on this assessment of available evidence, we designed a randomized, placebo-controlled clinical trial, on which we will further elaborate in the "Methods/ design" section and "Discussion" section.

METHODS/DESIGN

Overview

We designed a robust, multi-center, double blind, double-dummy, cross-over, randomized, placebo-controlled clinical trial with three study arms investigating transdermal fentanyl and sustained-release morphine. We hypothesize that both fentanyl and morphine provide a reduction of dyspnea which is greater than placebo, and that fentanyl has less side effects than morphine. A total of 60 patients with severe stable COPD and refractory dyspnea will be included in this study in ten Dutch hospitals.
Patients will be recruited at the outpatient clinic of each participating hospital by chest physicians. The study is registered at clinicaltrials.gov (NCT03834363), where a full list of participating hospitals can be found, and the protocol is approved by the UMCG Ethics committee.
Written informed consent will be obtained from all participants and the study will be performed in accordance with the Declaration of Helsinki.

Study duration and treatment

The study duration is 6 weeks for each participant, divided in three periods of 2 weeks. During each period the participant is treated for 11 days. During the first 3 days of every treatment period no study medication is used, to wash out medication of any previous treatment period. The fentanyl patches are dosed 12 μg/h and changed every 3 days. The morphine sustained-released capsules are dosed 10 mg b.i.d. Both an antiemetic (metoclopramide 10 mg as needed, up to thrice daily) and laxative (macrogol/electrolytes 13.7 g, started once daily, more or less sachets as needed) are prescribed. In total, there are four study visits. A complete study flowchart can be found in Fig. 6.1. After the end of the study treatment patients can discuss with their chest physician whether they would like to cntinue with low dosed morphine or transdermal fentanyl. At the time of this decision, the participants and physician are still blinded to the study treatment.

In- and exclusion criteria

All in- and exclusion criteria can be found in Table 6.2. In general, patients with COPD Gold class III or IV and a modified Medical Research Council score (mMRC) ≥ 3 who perceive dyspnea despite optimal standard therapy according to GOLD and the Dutch guideline for diagnosis and treatment of COPD can be included. If there is comorbidity substantially contributing to the breathlessness, for example severe heart failure, patients are excluded. Participants who have a moderate or severe exacerbation (requiring oral corticosteroids, antibiotics and/or hospital admission) during participation are discontinued from the trial. If they are stable for 8 weeks after recovery from the exacerbation, they are allowed to restart the study once more.

Outcome measurements

The primary outcome measurement is change in mean daily dyspnea sensation as measured on the numeric rating scale for Dyspnea[26]. Secondary outcome measurements are change in worst daily dyspnea sensation, health-related quality of life, anxiety, sleep quality, occurrence of respiratory depression and side effects, patient preference and continued opioid use. A more extensive description of theoutcome measures can be found in Table 6.3. Patients who drop out will be followed as much as possible for vital status, hospitalization, and start of open label opioids during the intended 6 weeks period of the study.

Randomization and unblinding

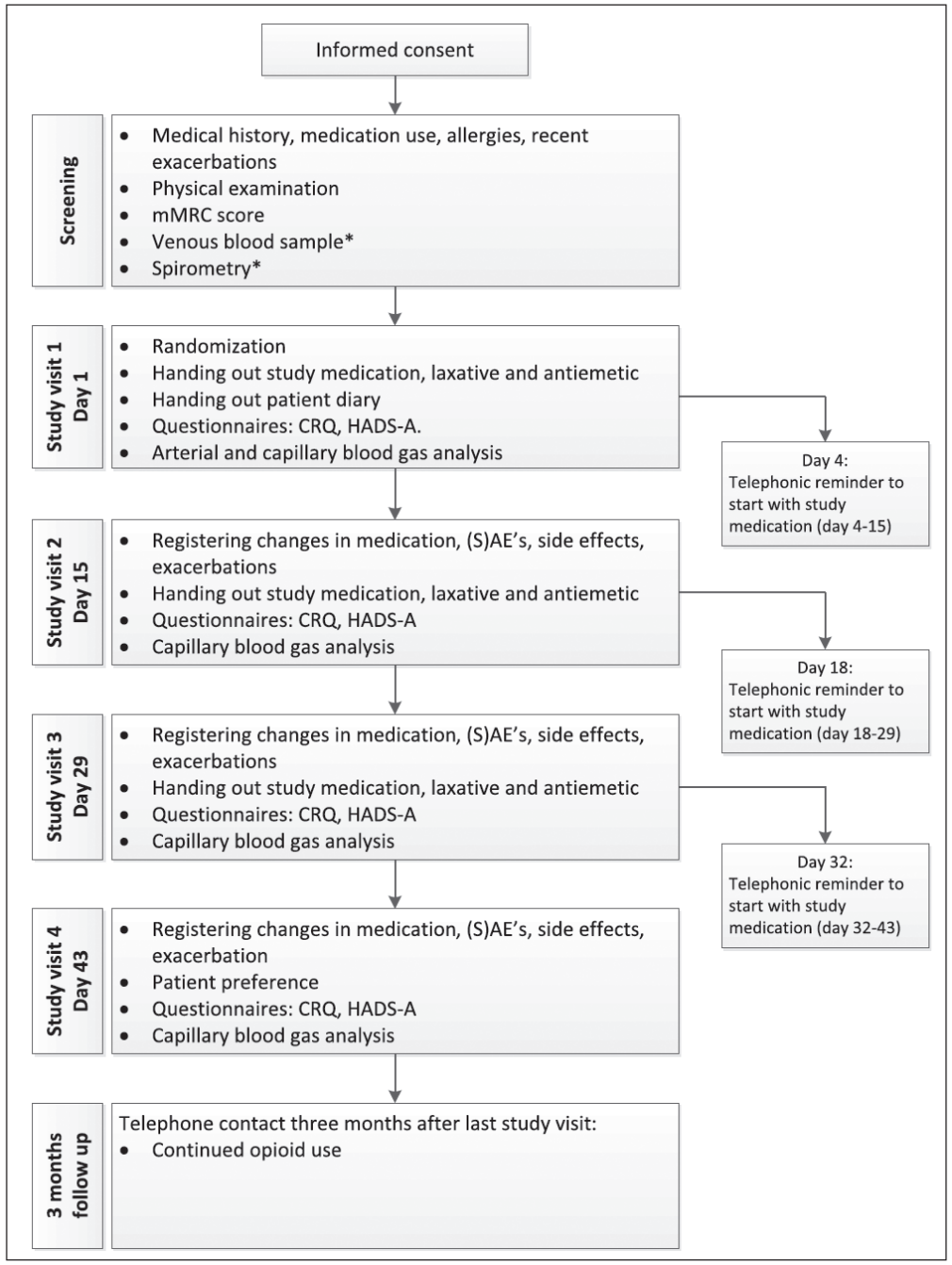
Randomization is tailor made for this study using a web based program (ALEA® DM version 17.1). Randomization can be performed online by the research team of each participating hospital. Participants will be randomized equally between the six possible treatment sequences, stratified for study location. Unblinding only occurs in the case of patient emergencies and at the conclusion of the study. Health authorities will be granted access to unblinded data if needed. The pharmacist on call of each participating hospital can unblind a participant using the web based program if requested by the researcher because of a patient emergency.

Statistical analysis

For the power calculation the difference in primary endpoint between fentanyl and placebo was used. The Minimal Clinical Important Difference (MCID) for the NRS score is 1 point, the standard deviation is 2.0 points[31]. With a two-sided alpha = 0.05 and a power of 0.90 in a cross-over design, 44 participants who complete the study are needed. Because this is a fragile patient group, we will aim to recruit 60 participants.

The primary endpoint analysis will be on an intention to treat basis and therefore all patients randomized.The primary endpoint is the NRS mean dyspnea score which we will treat as a continuous variable for day $^{7\text{-}14}$. This will not be calculated if less than 2 days are available. Since it is a three way crossover, the data for the available periods will also be used of not all periods were completed. No imputation will be used for the primary endpoint. There will be two comparisons: the difference in the mean dyspnea score of day $^{7\text{-}14}$ for fentanyl versus placebo and formorphine versus placebo. In this way,

Figure 6.1 Study flowchart



mMRC modified Medical Research Council Score, CRQ chronic respiratory questionnaire, HADS-A hospital anxiety de pression
*score-anxiety, (S)AE (serious) adverse event. *Unless already performed in the 6 months before screening*

the risk of any remaining effect from the previous treatment periods influencing the outcome will be optimally reduced.
The analysis will be by Student's t-test. The analyses of secondary endpoints will be done by Student's t-tests (or non-parametric tests where needed) or chi square, following the same scheme of main comparisons as for the primary endpoints. The analysis of side effects will be done by comparison of proportions of side effects by chi square tests between all three arms. Composite questionnaire data will be primarily analysed by total sum scores. Additionally, per protocol analyses will be performed. The study is not powered to determine equivalence of dyspnea relief of fentanyl compared to morphine: that comparison will consist of descriptive statistics only.

Safety

All (serious) adverse events will be monitored. The sponsor will report serious adverse events (SAEs) through the Dutch web portal ToetsingOnline to the accredited Ethics committee that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximumof 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events. This is a short term study with 60 patients, entered parallel in a multi-centre study. Therefore, and since opioids in the form of morphine are in the guidelines, we will not perform interim analyses, even though the patient population of patients with severe COPD and in a palliative setting is at increased risk of death. For the same reasons, no Data Safety Monitoring Board (DSMB) will be instituted.

Study timeline

The study has started in November 2019. At this point the first participant was included at the University Medical Center Groningen. For the other participating hospitals the start of inclusion was delayed by one or more months because of a delay in the production of research medication and a delay in the issuing of a permit for scientific research with opioids for the participating hospital pharmacies. Unfortunately, starting March 2020 the inclusion was alternately put on hold or restricted in each participating hospital due to the COVID-19 pandemic.
We aim to include all patients by the end of 2021, but whether this will be achieved is strongly depended on the course of the COVID-19 pandemic.

DISCUSSION

Optimal reduction of dyspnea in patients with severe COPD is an important way to improve quality of life, yet can be very challenging. From our assessment of the literature, we found that even though opioids have found their way into COPD guidelines as a treatment option for refractory dyspnea, the evidence base can still be considered inconclusive. Furthermore, the majority of research has focused on morphine and we identified no placebocontrolled RCT investigating transdermal fentanyl. However, trials investigating fentanyl in the short-acting form, suggest that fentanyl could give a reduction of dyspnea[32, 33]. Additionally, studies on pain treatment indicate that patients may prefer transdermal fentanyl and experience less side effects in comparison to oral morphine [34].

Table 6.2 In- and exclusion criteria

Inclusion criteria
Age ≥ 40 years
Read, understood and signed the Informed Consent form
COPD GOLD class III or IV, according to GOLD criteria
Post-bronchodilatation FEV1/FVC ≤ 70% and FEV1 < 50% pred.*
Complaints of refractory dyspnea as established by patient and doctor
mMRC score ≥ 3
Life expectancy of ≥ 2 months
Optimized standard therapy according to Dutch LAN guideline for diagnosis and treatment of COPD
Exclusion criteria
Other severe disease with chronic pain or chronic dyspnea (a non-susbstantial component of left sided heart failure is acceptable)
Current use of opioids for whatever indication
Allergy/intolerance for opioids
Psychiatric disease, not related to severe COPD
Exacerbation of COPD 8 weeks prior to inclusion or between screening and randomization
Problematic (leading to medical help or social problems) substance abuse during the last 5 years
Active malignancy, with the exception of planocellular or basal cell carcinoma of the skin
eGFR < 15 ml/min*

**Measured within 6 months of screening*
COPD chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 s, FVC forced vital capacity, GOLD global initiative for chronic obstructive lung disease, LAN Lung Alliance The Netherlands, mMRC modified Medical Research Council Dyspnea Scale, eGFR estimated Glomerular Filtration Rate

Table 6.3 Outcome measurements

	Measurement	Frequency of measurement
Primary outcome measure		
Change in mean dyspnea sensation	Numeric rating scale [26]	Once daily in patient diary
Secondary outcome measures		
Change in worst dyspnea sensation	Numeric rating scale [26]	Once daily in patient diary
Change in Health-Related Quality of Life	CCQ [27]	Once daily in patient diary
	CRQ [28]	During each study visit
	CRQ-mastery domain	During each study visit
	HADS-A [29]	During each study visit
	Open en named side effects	Once daily in patient diary and asked during study visits
Anxiety	Capillary blood gas analysis	During each study visit
Side effects	Numeric rating scale [30]	Once daily in patient diary
Change in hypercapnia, HCO_3 and pH	Asked during the final study visit	Once
Change in sleep quality	Asked 3 months after the end of study	Once
Patient preference		
Continued opioid use		

CCQ clinical COPD questionnaire, CRQ chronic respiratory questionnaire, HADS-A hospital anxiety and depression scale—anxiety subscale

Therefore, we believe that our current multi-center, double blind, cross-over, placebo-controlled study design to investigate sustained-release morphine and transdermal fentanyl for refractory dyspnea will provide valuable information on patient preference and the effectiveness of transdermal fentanyl and sustained-release morphine for refractory dyspnea in COPD.

By choosing a cross-over design for this study the participant is his or her own control, thus reducing the variability and the number of patients needed to participate. Additionally, this design helps to get a better impression of patient preferences. On the other hand, because of the cross-over design the treatment duration is 6 weeks instead of 11 days (which it would be if this study had a parallel design). This prolonged study duration will most likely increase the risk of participants that have to be discontinued from the trial because of the occurrence of COPD exacerbations, which occur frequently in advanced COPD. For this reason we aim to include 60 participants, which is sixteen more than the 44 participants calculated from the power analysis which need to fully complete the study. Furthermore, patients experiencing an exacerbation will discontinue the trial, but may be included once more if they are clinically stable for at least 8 weeks.

There are indications that prescription of opioids for refractory dyspnea in COPD can be a loaded topic for both patient and doctors, amongst others because of associations with terminal disease, possible adverse effects and addiction[10]. Although this has not been formally investigated in patients, we believe education is important to address any questions or worries patients may have regarding opioids. Therefore, both an animated short film for patients and their loved ones on facts and myths about opioids (developed by Indiveo B.V.) as well as an information leaflet with the same content are tested during our study. At the end of the trial, feedback from the participants will be used to adjust the animation and leaflet and these will be made widely available for patients with COPD. Additionally, both patients and physicians participating in the study are asked to share their experiences with opioids for refractory dyspnea in COPD during regional congresses and meetings.

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Part 4

On non-pharmacological breathlessness management in severe COPD

Chapter 7

Part 4

Treatment of anxiety in COPD with cognitive behavioral therapy

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ABSTRACT

A major part of COPD patients suffers from anxiety. The presence of an anxiety or stress disorder compromises their quality of life. Anxiety and (posttraumatic) stress disorders may be treated with cognitive behavior therapy (CBT). CBT encompasses different treatment interventions and protocols. Some of these interventions have been investigated to treat anxiety in patients with COPD. Those that have been proven to be effective, should be offered to COPD patients with anxiety. Examples are: education about symptoms in COPD (mostly dyspnea) and the bodily anxiety response; education about the positive and negative anxiety and breathing circle; breathing, posture and relaxation exercises; identification and correction of catastrophic thoughts; setting goals and planning activities (behavior activation) and pacing.

Many people with COPD suffer from symptoms of anxiety. But their practitioners are often unaware of this. That's unfortunate, since patients are likely to benefit from cognitive behavioral therapy.

Anxiety is common in patients with chronic obstructive pulmonary disease (COPD). The prevalence is significantly higher than with other diseases: approximately between 10 and 49%[1]. Yet an 'anxiety or mood disorder' diagnosis is missed in about half of the patients[2]. Patients often do not mention their fear because they do not link it to COPD, they are ashamed of it, or they fear that if they speak about it, the anxiety will increase. The relationship between anxiety and shortness of breath deserves more attention, both among COPD patients and their practitioners. Shortness of breath can lead to a fight-or-flight response through activation of the sympathetic nervous system. A tachycardia with accelerated, shallower breathing develops, which can trigger a panic attack[3]. This altered breathing pattern is particularly unfavorable in COPD[4] Patients with COPD need more time to exhale than healthy people because their airways tend to collapse on exhalation. After incomplete exhalation, air gets trapped in the lungs, leading to breathlessness due to a decrease in vital capacity. If patients have anxious thoughts as a result, a vicious cycle occurs that may be difficult to break[5,6]. The patient may start to avoid exertion, which leads to deconditioning, so that the patient becomes more breathless during exercise, which triggers anxiety, et cetera. After that, the physical symptoms and the affective response are difficult to distinguish. Therefore, treatment with bronchodilators alone is insufficient: attention needs to be given to the psychological domain of the illness.

Individual cognitive behavioral therapy (CBT) is one of the first steps in the treatment of an anxiety disorder[7]. CBT is a treatment in which techniques from cognitive therapy (thought redirection) and behavioral therapy (exposure) are used. CBT has a specific protocol for each psychological complaint or disorder. However, the effectiveness of the Dutch protocol for panic disorder has never been studied in COPD patients[8]. Moreover, CBT practitioners in mental health care (GGZ) cannot be expected to have knowledge on mechanisms of breathlessness in COPD, which hinders effective treatment.

CBT FOR ANXIETY IN COPD

Three large, randomized studies have now been conducted with anxiety in COPD as an outcome measure. The studies examined individual CBT in patients with COPD with clinically relevant anxiety symptoms. There were at least 100 participants in the intervention group. We briefly discuss these studies here and discuss the different CBT techniques that were used later.

The first is a British randomized study from 2014[9]. In this study, anxiety symptoms improved significantly after 6 months. 112 COPD patients used a worked CBT-based shortness of breath manual for five weeks. They received the explanatory book during a home visit from a nurse. Afterwards there were two more phone calls. The control group worked independently from information leaflets on anxiety from the British Long Foundation. After 12 months, the emergency room visits were with 42% reduction in the group that received the CBT intervention, while the group that received the information leaflets had 16% more frequent hospital visits. The chance that a participant from the intervention group visited the emergency room was almost twice as low as the chance that someone from the control group did. Hospital admissions also decreased in the intervention group.

The second study that showed that CBT reduces anxiety symptoms in COPD is an American study from 2017. In this randomized study, 112 patients were offered eight sessions of CBT[10]. On average, the patients followed four sessions. Compared to the control group receiving standard care, the CBT participants improved with regard to anxiety symptoms after four months of treatment ($p < 0.001$; $d = 0.37$). The effects persisted after eight and twelve months of follow-up.

The third study, a British study published in 2018, showed that CBT by nurses is cost-effective. Treated patients visited the ED less often 12 months after treatment and were hospitalized less frequently[11]. Treatment consisted of two to six sessions of CBT by a pulmonary nurse. The average was four sessions. There were 129 COPD patients in the intervention group; the control group received self-help leaflets. Both interventions were effective, but anxiety symptoms decreased significantly more in the CBT group (mean difference in improvement after three months 1.52; 95% CI: 0.49-2.54; $p = 0.003$). Thus, a short-term CBT of three to eight sessions may be effective for anxiety in COPD, although the magnitude of the effect was limited. These studies all offered treatment specifically for COPD. The given treatment differs from the Dutch panic disorder protocol[8]. The researchers used techniques from the handbooks of several smaller studies in which the treatment had been shown to be effective for anxiety in COPD. Below we describe these CBT techniques.

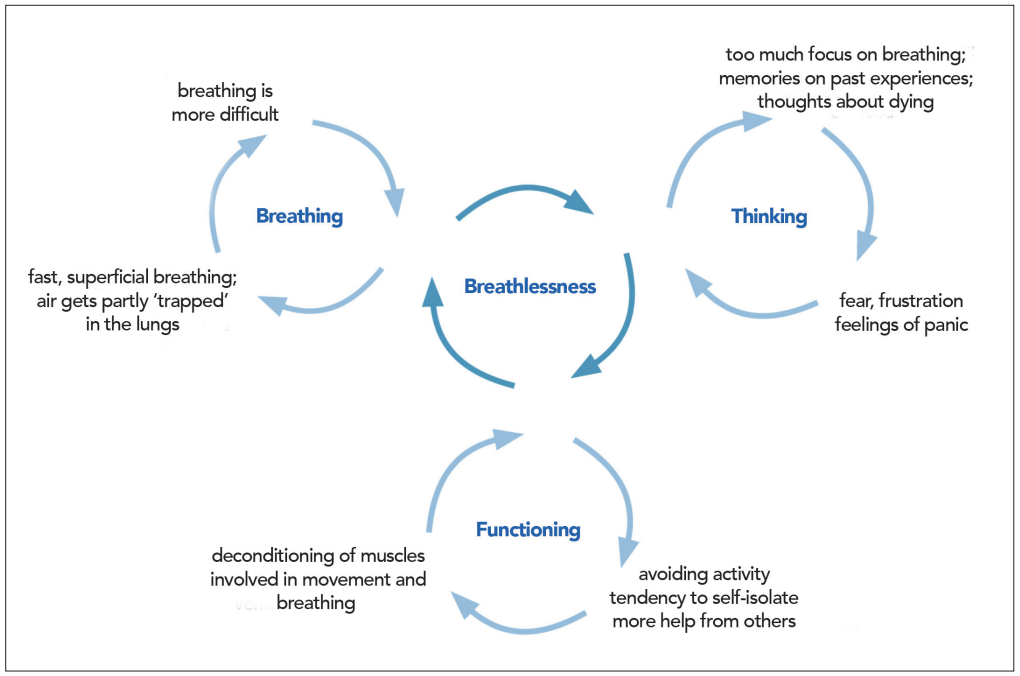
EFFECTIVE CBT TECHNIQUES

Education

Explanation of the differences and similarities between the symptoms of COPD and the body's fear response has been shown to significantly reduce anxiety after just one or a few sessions[12]. The physical effects of fear and the fight-flight-freeze response should be

addressed, but also about alarm symptoms (fever, increased sputum production) and when to contact the doctor [9,13]. In order to provide this information, the CBT practitioner must have knowledge of the symptoms of an exacerbation. Illustrations of a positive and negative breathing cycle (trigger, bodily sensation, thoughts, feelings and behaviors) are helpful, according to patients, because they learn to recognize a dysfunctional breathing pattern and gain insight into how they can influence this pattern for the better. This gives a sense of control and makes the fear more manageable (see figure 7.1)[14]. An explanation about the origin of breathlessness is also essential. Usually, the cause is not lack of oxygen, but the fact that less air flows in and out of your airways. The patient must increase the work of breathing, especially during exhalation, which results in breathlessness.

Figure 7.1 The negative breathing cycle



Shortness of breath can cause anxiety and induce a vicious cycle. This development can be reversed through education, activation and relaxation, posture and breathing exercises. (Source: Spathis A, et al. The breathing, thinking, functioning clinical model. NPJ Prim Care Respir Med. 2017;27:27)

Exercises

Relaxation, posture and breathing exercises can increase control over breathing [9]. This allows the patient to break the negative vicious breathing cycle.
In breathing exercises, for example, think of the 'pursed-lip breathing', keeping the airways open; prolonging the exhalation to diminish hyperinflation; and conscious brathing with the diaphragm, in which the patient places the hands on either side of the navel in a relaxed position and feels the abdomen rise on inhalation [9,11,13,15]. It is essential that the practitioner knows which breathing exercises are recommended in COPD: deep inbreaths are not recommended, the focus should be on the exhalation.

Relaxation exercises include guided imagery [9,10,16]. Furthermore, distraction can cause patients to focus on something other than breathing; hyperfocus can cause anxiety and shortness of breath. Patients can distract themselves in many ways: for example, by counting back from one hundred to zero in increments of seven, by listing places or countries they have visited in their lives, or by imagining that they are in a beautiful place [9,11]. Distraction is less effective in advanced disease with severe symptoms [17].

Redirecting Thoughts

Shortness of breath can evoke negative thoughts in patients. Think of hasty generalization ('last time I was short of breath I was with friends, I won't go there now'), mind reading ('when people see that I am gasping for breath, they will think: "stop smoking so much"') and disaster predictions ('I'm going to suffocate')[9-11,13,15,16]. Examining and challenging these thoughts can help reduce anxiety. Patients can practice this independently.
The exercises are aimed at recognizing, naming and clarifying thoughts. Catastrophic thoughts are challenged by looking for counter-arguments.
In order to be able to properly help people with COPD with these exercises, it is essential that the practitioner knows the disease well enough. All patients interviewed about this intervention spontaneously mentioned fear of death and/or suffocation (14). This fear of choking is an important example of a catastrophic thought that can be treated with CBT. Although many COPD patients die from their disease, there is no choking as such. After all, the trachea does not get blocked; even during a breathlessness crisis, air will still move back and forth. When an exacerbation of COPD leads to death, there is hypercapnia. In most cases, this induces a lowering of consciousness instead of a feeling of suffocation.

Activation

Activation techniques are used when, in addition to anxiety, there is also inactivity or depressive symptoms. These are the techniques of 'goal setting' and 'planning enjoyable activities'[9-11]. By scheduling and recording activities during the day, inactivity is reduced and condition improves. These techniques are already common in the first phase of the Dutch depression protocol [17].
In the case of COPD, the patient should learn to slow down the pace at which activities are performed ('pacing')[11,13,15,16]. Patients tend to perform strenuous activities hurriedly in order to 'get them over with'. Also, people with COPD usually do not feel short of breath at rest, causing them to forget that they need to do the activities more slowly than they used to. By slowing down and 'chunking up' activities, patients can get more done with less breathlessness[18].
With knowledge of COPD and CBT, health care professionals may advise and treat COPD patients with anxiety. In several studies, the techniques were performed by (pulmonary) nurses[9,11,13]. CBT may be a realistic alternative to prescribing benzodiazepines. Benzodiazepines only have a short-term effect, cause habituation with prolonged use and have the disadvantage of reduced coordination and the risk of falling. CBT does not have these drawbacks. Optionally, CBT can be combined with SSRIs; (limited) research has shown that SSRIs are effective and safe for anxiety in COPD [19,20].

CONCLUSION

Anxiety is a common complaint in COPD. Unfortunately, roughly half of all cases go undiagnosed. Therefore, health care professionals should specifically ask about fear, tension or worry, preferably using a screening questionnaire, such as the Hospital Anxiety and Depression Scale (HADS).

A number of specific CBT techniques have been proven effective in COPD. However, in-depth knowledge about COPD is limited within mental health care. A practitioner who does not know that a deep inhalation in a patient with COPD can lead to increased shortness of breath and that the exhalation must be prolonged, will not achieve sufficient effect. The practitioner should also know that certain catastrophic cognitions of the patient ("I need more oxygen," or "I'm going to choke one day") are incorrect.

There is a need for a Dutch treatment protocol that describes specific CBT techniques for COPD and that can be applied by practitioners who have a lot of experience with COPD, such as (pulmonary) nurses, respiratory physiotherapists and practice nurses.

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Chapter 8

Part 4

"When I am breathless now, I don't have the fear that's linked to it."

A case series on the potential of EMDR to break the dyspnea-anxiety cycle in COPD

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ABSTRACT

Background

Expectations can enhance the intensity and the neural processing of breathlessness. Previous breathlessness episodes may influence the perception of subsequent episodes because of psycho-traumatic consequences. In post-traumatic stress disorder (PTSD), eye movement desensitization and reprocessing (EMDR) is the therapy of choice.

Aims and objectives

We explored the hypothesis that EMDR in patients with chronic obstructive pulmonary disease (COPD) and previous severe breathlessness episodes, improves breathlessness mastery by decreasing the anxiety component.

Methods

As we found no literature on previous research on this subject, we undertook a qualitative case series on four patients with COPD GOLD 4/D and refractory breathlessness who wished to undergo EMDR for psychotraumatic breathlessness episodes. Amongst others, we used the Chronic Respiratory Disease Questionnaire (CRQ) before and after EMDR, and semi-structured, face-to-face, in-depth interviews.

Results

All patients had between three and five EMDR sessions. On CRQ, subset mastery, three patients had a large improvement and one patient a moderate improvement. On subset emotional functioning, three patients showed a large improvement and one showed no change. All patients made a distinction between 'regular' breathlessness and breathlessness intertwined with anxiety. They all stated that the anxiety component of their breathlessness diminished or disappeared. All four would recommend EMDR for other COPD patients.

Conclusions

There is ground for a randomized controlled clinical trial to test the effects of EMDR on breathlessness mastery in a subset of COPD patients with previous severe breathlessness episodes and high levels of anxiety.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an often progressive and life-threatening lung disease. It is the third leading cause of death in the world [1] and its prevalence is increasing worldwide. The cardinal symptom of COPD is breathlessness, which has a large impact on the quality of life in the majority of patients [2].Breathlessness in COPD is known to correlate poorly with pulmonary function tests such as forced expiratory volume in the first second (FEV_1) [3]. This discordance between physiological disturbances and the patient's experience underscores the role of the brain in processing sensory signals from the respiratory system. Both mood and expectations are major contributors to the function of the brain networks that generate breathlessness perception [4].Indeed, the brain generates predictions about the sensations the body should be feeling, often fed by prior experiences and contextual cues. For example, a staircase that has led to a breathlessness crisis before, may induce the same sensations in a patient before even starting the ascent [5].

As we have learned from patient experts, a breathlessness crisis is a paralyzing experience in which nothing is present except the terrible need to get air in [6,7]. In a listing of dozens forms of torture, according to the ratings of perceived distress and uncontrollability, asphyxiation ranked first with respect to perceived uncontrollability and second with respect to perceived distress [8].Of note, the defining characteristic of a psychotraumatic event is its capacity to provoke fear or helplessness in response to the threat of dying. It is likely that patients who experience breathlessness crises share characteristics with those who suffer from post-traumatic stress disorder (PTSD) [9]. Indeed, patients with recurrent COPD exacerbations have an increased risk of PTSD symptoms [10].

Unfortunately, in patients with severe COPD, distress not only is caused by airflow obstruction but may also contribute to it. Distress may lead to rapid, shallow breathing. This breathing pattern leads to air trapping, thus aggravating the breathlessness because of expiratory airway collapse [11]. Thus, the learning experience of a breathlessness crisis is susceptible for reinforcement, when a subsequent episode of breathing discomfort sets a "dyspnea-anxiety-dyspnea cycle" in motion.

Although our knowledge of the role of the brain in breathlessness perception has greatly increased in the last decade, this has not yet led to clinically applicable improvements for patients. In randomized controlled trials neither antidepressants nor anxiolytic drugs have been proven to alter the experience of patients with refractory breathlessness [12,13]. However, the viewpoint that traumatic breathlessness episodes may lead to PTSD symptoms which aggravate breathlessness, has not been explored before.

The therapy of choice for PTSD, according to the World Health Organization (2013), is Eye Movement Desensitization and Reprocessing (EMDR). EMDR is a psychotherapeutic approach, developed over 30 years ago to treat traumatic memories and their associated stress symptoms [14]. Its effectiveness in PTSD has been proven in several meta-analyses [15,16]. EMDR combines well-establised psychotherapeutic techniques such as directive exposure to intrusive memories and breaking avoidance with bilateral sensory stimulation. (such as left-right eye movements or tapping on the knees) while the patient concentrates on the memory. According to the theory of adaptive information processing (AIP) that underpins EMDR, overwhelming psychotrauma causes physiological responses to interfere with information processing. As a consequence, a distressing event is stored

in a raw, state-specific form. Activation of pathogenic memories can lead to symptoms such as flashbacks. Dysfunctionally stored memories are the focus of EMDR procedures. Supposedly, the vividness and emotionality of the pathogenic memory decreases during eye movements or other dual tasks, so that afterwards the memory can be reprocessed without the accessory stress and anxiety [17].
Patients with COPD are sporadically referred to undergo EMDR because of psychotraumatic events in their past. We hypothesize that EMDR in patients with COPD and previous severe breathlessness episodes improves breathlessness mastery by decreasing the anxiety component.

METHODS

A thorough search of the literature was performed on EMDR for COPD-related breathlessness (search terms and strategy described in supplement). We found no previous research on this subject, although two case reports concerning the positive effect of EMDR on breathlessness due to other conditions – pediatric asthma and amyotrophic lateral sclerosis - were retrieved [18,19].
Therefore, we undertook a qualitative case series on four patients with COPD GOLD 4/D and refractory breathlessness who wished to undergo EMDR for psychotraumatic breathlessness episodes. The case series employed mixed methods of quantitative outcome assessment and qualitative interviews. In our large teaching hospital, we consecutively included patients between December 2019 and March 2021, with the following inclusion criteria:

- COPD as diagnosed by a chest physician;
- refractory severe breathlessness, defined as Modified Medical Research Council (mMRC) dyspnea scale 3-4, persisting despite optimal treatment;
- referred by their chest physician for EMDR because of one or more stressful episodes in their past related to breathlessness;
- willingness to be interviewed after the intervention.

Exclusion criteria were:

- inability to read and write Dutch (for questionnaires);
- inability to visit the hospital for appointments.

Patients were recruited from the pulmonary outpatient clinic.
The study protocol was approved by the Medical Ethics Review Committee of Amsterdam University, which confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to the current study.

Intervention

All patients were treated with the EMDR standard protocol by the same psychiatrist (JG), who has experience with administering EMDR since 2015 and has been an EMDR practitioner since 2019.

Data collection

The following questionnaires were used before and directly after the intervention:

- Clinical COPD Questionnaire (CCQ). This is a simple 10-item, health-related quality of life questionnaire. It consists of three subdomains: symptoms, functional state and mental state. Items are scored on a Likert scale (range 0–60). The final score is the sum of all items divided by 10; separate scores for all three domains can be calculated. Higher scores indicate a worse health status. The minimal important difference of the CCQ total score is 0.4. [20]
- Chronic Respiratory Disease Questionnaire (CRQ). This questionnaire measures 4 domains, namely dyspnea, fatigue, emotional function and mastery, using a 7-point modified Likert Scale. Higher scores indicate better health-related quality of life. A change in the score of 0.5 on the 7-point scale, reflects a clinically significant small change. A change of 1.0 reflects a moderate change and a difference of 1.5 repre sents a large change. [21]
- Hospital Anxiety and Depression Scale (HADS). HADS is a 14-item scale with seven items each for anxiety (HADS-A) and depression (HADS-D) subscales. Scoring for each item ranges from zero to three. A subscale score above eight denotes clinically rele vant symptoms of anxiety or depression [22].
- 48-item Symptom Questionnaire (SQ48). SQ48 is a self-report measure of psycholo gical distress, using nine subscales (normal values between brackets) {range between curly brackets}: Depression (0-8){0-24}, Anxiety (0-11){0-24}, Somatization (0-8){0-28}, Agoraphobia (0-2){0-16}, Aggression (0-5){0-16}, Cognitive problems (0-11){0-20}, Social Phobia (0-9){0-20}, Work functioning (this item was not used since none of our patients were working), and Vitality (9-24){0-24} [23.]

All patients reported their experience regarding psychotraumatic breathlessness experiences, their impact on their quality of life, and EMDR, in semi-structured, face-to-face, in-depth interviews. The interviews were all held after the EMDR, were audio-recorded and transcribed verbatim.

Analysis

The scores of CRQ, CCQ, HADS and SQ48 were calculated before and after EMDR. Only descriptive statistics were used. Two researchers (KM and YE) independently open coded the first interview line by line with direct content analysis and compared and discussed the codes until consensus was reached. The remaining three interviews were coded by one researcher (KM). Next, two researchers (KM, YE) grouped the codes into themes and sub-themes. The coding process was performed using Atlas.ti software v.8 (http://atlasti.com; Atlas.ti Scientific Software Development GmbH, Berlin, Germany).

RESULTS

During the study period (between December 2019 and March 2021), nine patients with severe COPD, severe breathlessness and a wish to be referred for EMDR were assessed for inclusion. Of those, five were not included for the following reasons: one did not consent to be interviewed, two wanted EMDR for non-breathlessness related events, one

declined from EMDR after the intake, and one died of an acute exacerbation of COPD (AECOPD) shortly after referral. The other four eligible patients were included in the case series. The most relevant scores of their questionnaires before and after EMDR are presented in table 8.1.

Table 8.1 Outcomes of most relevant questionnaires before and after the intervention.

	Case 1	Case 2	Case 3	Case 4
SQ, anxiety, before EMDR	12	16	16	20
SQ, anxiety, after EMDR	7 *	14 *	15 *	8 *
HADS-A, before EMDR	Missing	16	17	9
HADS-A, after EMDR	Missing	12 *	11 *	4 *
CCQ, mental, before EMDR	3	5.5	4	3.5
CCQ, mental, after EMDR	1 *	3.5 *	3 *	2.5 *
CRQ, emotional, before EMDR	3.8	2.3	2.7	3.7
CRQ, emotional, after EMDR	5.8 *	5.3 *	2.7	5.2 *
CRQ, mastery, before EMDR	2.3	2.5	2.5	3
CRQ, mastery,after EMDR	5.3 *	5.8 *	4.3 *	4.3 *

Legend: For SQ subset anxiety, values above 11 suggest high levels of anxiety. For HADS-A, values above 8 suggest high levels of anxiety. For CCQ, lower scores indicate a more favorable health status. For CRQ, higher scores indicate a more favorable health status.
**clinically relevant change*

Case 1
Patient E., female, aged 63, was referred for EMDR after hospitalization for an AECOPD because of fear for breathlessness. During her intake session, she described a deep fear of suffocation, panic attacks related to her COPD, and fear to go out of the house without taking a benzodiazepine. She had been claustrophobic since she had been rolled into a carpet as a four-year-old by other children and could not get out. After her intake session with the psychiatrist, she was diagnosed with agoraphobia and panic disorder. Previously, she had been diagnosed with carcinophobia. She used oxazepam 10 mg three times daily. She did not drink alcohol.
EMDR was provided, targeting memories and disaster scenarios. The memories were: being breathless, breathlessness in the shower, being rolled into a carpet. The mental images or disaster scenarios were: dying by suffocation, the idea of having cancer in her throat, sitting on a chair unable to move, hearing the doorbell ring unexpectedly. She had five sessions (between December '19 and February '20).
On CCQ, measured before and after EMDR, she showed no (significant) change on symptoms or functioning, but a large improvement (2 points) in mental status. Unfortunately, no HADS was measured in this patient. On CRQ, subscales dyspnea and fatigue remained unchanged but subsets emotion and mastery both showed a large improvement of 2 points. Regarding SQ48, there was a large improvement in anxiety (5 points) and some improvement in vitality. Other subsets remained unchanged.

Case 2
Patient B., male, aged 69 years, asked for referral to undergo EMDR, because of fear of suffocation. He avoided activity for fear of breathlessness and had constant thoughts of suffocating. In his life, several important events happened that concerned breathing: there had been two events of near drowning when he was young; he had caused a fire in his garage (before he had COPD), and he had had a severe breathlessness crisis in his car due to COPD. Of those events, he deemed the breathlessness crisis in his car essential to his anxiety. Previously, he had been diagnosed with depression, agoraphobia and panic disorder. He took oxazepam (5 mg) PRN. He did not drink alcohol.
EMDR targeted memories and disaster scenarios. The memories were: breathlessness crisis in the car and becoming breathless while walking to car. Disaster scenarios were: dying while in the shower, becoming unable to drive his car, panic attack in the presence of a stranger, and becoming breathless in a crowded cinema. He had four EMDR sessions (between April and May '20).
On CCQ, measured before and after EMDR, he showed an improvement on all subsets (0.8 points on symptoms, 0.5 points on functioning and 2 points on mental status).
He had high scores on HADS-A before treatment, which declined significantly with 4 points but not below 9. Regarding SQ48, he showed some improvement on most subsets, except vitality.

Case 3
Patient P. male, aged 79, asked for referral for EMDR because he had heard that it could be effective. He suffered from fear of suffocation and described overwhelming anxiety when he thought of breathlessness and of dying. He had no specific breathlessness episodes in his life, other than general breathlessness related to COPD. He used no psychotropic drugs and drank two units of alcohol per day.
EMDR was provided, targeting both memories and mental images or disaster scenarios. The memories were: Breathlessness during an exacerbation of COPD and the death of his father. Disaster scenarios: being strangled; dying, choking, while the hospital staff cannot help him. He had four EMDR sessions (between February and June '20). Part of the EMDR was done through video calling because of the COVID-19 pandemic.
On CCQ, measured before and after EMDR, he showed a deterioration in symptoms (0.5 points), but a significant improvement in mental status (1 point); functioning remained unchanged. HADS-A showed a great improvement (6 points) but stayed above 8.
On CRQ, subscales dyspnea and emotion remained unchanged, fatigue deteriorated (1.5 points), but mastery showed a large improvement (1.75 points). Regarding SQ48, he showed only a small improvement in anxiety and social phobia; the domains vitality and cognitive complaints deteriorated somewhat. Other subsets remained unchanged.

Case 4
Patient H., female, aged 65, had been referred for EMDR before because of fear of suffocation. During the intake, she gave a detailed description of the onset of AECOPD a year before the referral. During this breathlessness crisis, she was unable to wake up her husband. She experienced fear of suffocation, flashbacks and fear to leave the house. She had no previous psychiatric history but at the start of EMDR, PTSS was diagnosed.

She used one unit alcohol daily, took morphine 10 mg SR twice daily for breathlessness, and had recently started taking oxazepam 10 mg PRN.
Because of visual impairment, EMDR was provided with two vibration devices (buzzers). The target memories were the described breathlessness crisis, and a breathlessness episode she had experienced while taking a shower. She had three EMDR sessions (between March and May '21).
On CCQ, measured before and after EMDR, she showed a deterioration in symptoms, but a significant improvement in mental status and functioning (both 1 point). HADS-A declined with 5 points to a normal value. On CRQ, subscale dyspnea could not be assessed because the patient did not fill in that part of the questionnaire. She improved markedly on emotion (1.5 points), fatigue (2 points) and mastery (1.3 points). Regarding SQ48, she showed a great improvement in anxiety (12 points), agoraphobia (6 points, score normalized to 0), social phobia (4 points, score normalized to 0), somatic complaints (13 points) and depression (15 points, score normalized to 2). Nonetheless, she deteriorated on the domain vitality with 7 points.

Results qualitative interviews
The initial number of 101 codes could be merged into 18 categories, which were grouped into four themes: trauma, panic and anxiety, breathlessness and effect of EMDR.

Trauma
All four patients described psychotraumatic episodes related to breathing. For patient 1, the main event was being rolled into a carpet by other children when she was very young. She described how, since then, she was afraid of confined spaces and did not tolerate anything on her face. In her opinion, this event was more significant than the breathlessness she experienced because of her COPD.
The psychotraumatic breathing episodes described by the other three patients were mostly COPD related. Besides, patient 2 described two episodes of near drowning, as well as being in a fire in his garage, but felt that the breathlessness related to his COPD had much more impact.

> ***"The fire and the drowning were not that bad. But the stepping into the car… (….) I got a panic attack that made me rigid. (…) It was very oppressive and very frightening."***

Panic and anxiety
All four patients described high levels of anxiety related to breathing. One patient described how breathlessness would lead to shaking, suggesting a linkage with fear.

> ***"You feel how you can't breathe, or hardly. Or you start shaking. When I walk during physio, walk three times, I start shaking."*** (Patient 4.)

They described how certain events triggered anxiety: wind (patient 1), having a shower (patient 1, patient 2, patient 4), having to go to the toilet (patient 1), being alone (patient 2), going out (patient 2, patient 3). Moreover, all four patients described fear of suffocation. The idea of sudden breathlessness in a public space provoked anxiety in patient 2. Patient 1 described loss of control:

> ***"I get so breathless, it becomes a panic attack. Because you just can't control it anymore."*** (Patient 1)

Patient 2 and 3 described fear of dying.

> ***"Like a very nasty death struggle due to the breathlessness, a very painful affair. I could picture that in my mind."*** (Patient 3)

Patient 2 and 3 described an increase of anxiety after something witnessed in other patients (on the first aid or on the ward).

> ***"He was wheeled in and started arranging his euthanasia, while I was lying next to him. It got to me, it really did. It came really close. I got this panicky feeling, feeling of suffocating and not being able to come out of it. Some sort of stranglehold, I got."*** (Patient 3)

Of note, both patients 1 and 4 described being claustrophobic, both were afraid of confined spaces and did not tolerate anything on their face.

> ***"Yes, just don't let them touch my face or my head. And I am always on the outside of doors, and the doors must be open, you know."*** (Patient 4)

Breathlessness
Patient 1, 2 and 4 described frequent unpredictable breathlessness crises that were not triggered by exercise or an exacerbation. Patient 4 described how the memory of a sudden episode of breathlessness when she was sitting on a specific chair in the house, would come back when she sat in the same chair. Patient 2 described how an episode of breathlessness reminded him of the severe crisis he had while sitting in a car. Patient 2 described how breathlessness could be induced by thoughts:

> ***"When I go to bed at night, I think, oh I didn't get breathless, and then that's when I get it."*** (Patient 2)

Effect of EMDR
On anxiety
All four patients described being less anxious after EMDR. In all four patients, fear of suffocation had disappeared or greatly diminished. Patient 2 described that, since EMDR, he no longer feared a sudden breathlessness episode in a public space, and felt more confident to go out.

On breathlessness
Concerning breathlessness, all four patients made a distinction between 'regular' breathlessness and breathlessness with anxiety. They all stated that the breathlessness in itself did not change, but the intertwined anxiety diminished.

> ***"Because at a certain point, I was breathless all day, also because of the panic. Now I am breathless, but only when I do something. The normal breathlessness that comes with the COPD. That I can handle, by the way. Not always, but most of the time. Panic breathless you just can't handle. You try, but you can't."*** (Patient 1)

> ***"The breathlessness in itself did not change. Just the link with anxiety disappeared. The breathlessness is there, that won't disappear with EMDR. I still have that. When I am breathless now, I don't have the fear that's linked to it, like o my god here comes that stranglehold."*** (Patient 3)

> ***"The breathlessness is still there, but I deal with it differently, I tolerate it better. It's a different feeling. A lot less fear. Less panic."*** (Patient 2)

> ***"Usually when I have to go to the bathroom, I think o I have to go, o God o God. If only I don't get frightened, I think. (...) But at a certain point I thought, I have been to the bathroom three times without realizing it thinking or about it. O it helps. O, it helps!! I called my sister right away, it helps it helps. I have been to the bathroom three times!*** (Patient 1)

On coping with COPD
Patient 2 described how he was not bothered anymore about what other people think.

> ***"Those things I say, I am going to do things in stages, and I do not care a rap if anybody sits next to me and I get breathless. They know it, they will have to accept it. I don't have to think about them, they should be thinking about me."***

Patient 1, 2 and 4 described how they had changed their daily routines since EMDR, suggesting a better coping style.

> ***"For example, I have done the laundry and I need to bend over to take it out. Then I need to hang it. You can do it in stages, you can and you should. And I thought, if I just do it all at once, I get it over with. But I don't do that anymore, not since the EMDR." (Patient 1.)***

Recommendation for other patients
When asked whether they would recommend EMDR for other COPD patients, all four subjects answered positively. Patients 1 and 3 had already advised a fellow patient to try EMDR. Patient 2 noted that EMDR would not benefit all patients with COPD, only those who experience panic. Patient 4 stated that it was helpful for anxiety, but not for breathlessness.

Side-effects
Patient 1 mentioned some fatigue after EMDR. No other side-effects of the intervention (such as increased breathlessness during EMDR) were mentioned by the study subjects.

DISCUSSION

The present case series suggests a potential benefit of EMDR in a subset of COPD patients, who have experienced potential psychotraumatic episodes of breathlessness.
In the qualitative interviews, patients illustrated how such memories enhance and intensify the experience of breathlessness symptoms. Indeed, breathlessness could be triggered by a situation where a previous breathlessness crisis had taken place, or even by thoughts. All patients reported high levels of anxiety and described how breathlessness and anxiety were intertwined.
After three to five EMDR sessions, all four patients had a notable effect on the mastery domain of CRQ. EMDR decreased levels of anxiety (according to the interviews, SQ subset anxiety, and the HADS-A that was taken in three out of four patients). Interestingly, they all distinguished 'normal breathlessness' from 'panic breathlessness' after EMDR. They all stated that normal breathlessness wasn't altered by this intervention, which is illustrated by the fact that CCQ, subset symptoms did not improve in three out of four patients. However, the 'panic breathlessness' improved greatly. This supports our hypothesis that previous psychotraumatic breathlessness episodes play an important role in symptom experience, and maybe also in quality of life. Three out of the four patients were able to describe psychotraumatic breathlessness crises in detail (case 1, 2 and 4). According to the questionnaires, they had more benefit of EMDR than patient 3, who suffered from fear of suffocation but did not have a specific memory of a breathlessness crisis. This is in accordance with the leading explanation for the mechanism behind EMDR, in which an aversive memory is pivotal[17].
Interestingly, three out of four patients described how they had better ways to cope with their breathlessness after EMDR. This might also be a result of the psychoeducation that was given prior to EMDR referral (including the explanation that patients with COPD do not literally suffocate, because the airways stay open).
EMDR is a safe, well tolerated, fast and low-cost intervention that has rapidly been gaining popularity in the last decades (15). The fact that all four patients stated that they recommended the intervention for other COPD patients is telling. However, to assess its possible place in the management of breathlessness, a randomized controlled trial is necessary in which EMDR is compared to psychoeducation. Eligible patients should have severe breathlessness due to a chronic illness with episodic breathlessness (such as COPD or heart failure), high levels of anxiety and a vivid memory of a breathlessness crisis.

Strengths and weaknesses

To our knowledge, this is the first study exploring the possible effect of EMDR in breathlessness in COPD. The combination of semi-structured interviews and validated questionnaires has been helpful to explore this promising intervention and to strengthen our hypothesis.

The low number of included patients is a weakness. The number of four interviews is too low to reach saturation; indeed, every interview yielded new codes. We have tried to find more patients for our interviews via other therapists but did not succeed. Therefore, a prospective study should ideally have a mixed-methods design to further explore patient experience of this intervention. Furthermore, it is important to measure long-term effects which has not been done in this case series.

CONCLUSION

According to this case series, EMDR is a promising intervention in patients with refractory breathlessness in combination with anxiety, who have vivid memories of breathlessness episodes. Our findings validate the design of a randomized controlled clinical trial on this subject.

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Chapter 9

Part 4

Filling the Gap:
A Feasibility Study of a COPD-Specific Breathlessness Service

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ABSTRACT

Refractoy breathlessness is a devastating symptom in chronic obstructive pulmonary disease (COPD). Symptom-focused breathlessness services, involving palliative care teams, offer individualized support but are not yet widely available for people with nonmalignant disease among which COP D. Our primary aim was to demonstrate the feasibility of setting up a breathlessness service specifically for COP D patients within a respiratory outpatient clinic. Our secondary aims were to assess how many sessions patients need to complete the intervention; to obtain an indication of effect size (on the Chronic Respiratory Questionnaire (CRQ), subset mastery domain); and to evaluate patient and professional satisfaction. We conducted a non-randomized single-center feasibility study. Participants had COPD and refractory breathlessness. During at least one session with a respiratory nurse and a pulmonologist, and one session with a physiotherapist, patients learned nonpharmacological interventions to manage breathlessness. Of 34 screened patients, 19 were included.
All completed the intervention. A median of two clinical visits and two telephone calls were needed to complete the intervention. The mean improvement of 1.55 in CRQ, mastery domain, significantly exceeded the clinically important difference of 0.5. The service was rated as excellent by the eight patients who completed the survey. The health professional team gave positive feedback on the experience of delivering the intervention. Delivery of a breathlessness service for COP D outpatients with refractory breathlessness appears feasible, easy to implement in a respiratory outpatient clinic, and has the potential to be effective. A randomized controlled clinical trial is needed to test effectiveness and cost-effectiveness in this context.

INTRODUCTION

Chronic obstructive pulmonary disease (COP D) is a highly prevalent, life-threatening lung disease.The cardinal, debilitating symptom of advanced COP D is breathlessness, which persists in most patients, even when disease management has been optimized [1].

There is little correlation between physiologic parameters (such as airflow obstruction and gas exchange disturbances) and breathlessness. This is partly explained by patients' individual cognitive and affective responses to the sensory disturbance [2]. For instance, anxiety leads to rapid, shallow breathing, resulting in an increase in hyperinflation and thus, worsening of the symptom [3]. Due to this anxiety-dyspnea vicious cycle, many patients with advanced COP D experience unpredictable episodic breathlessness[4]. Consequently, the complexity of breathlessness in COP D patients warrants an individualized, multidisciplinary intervention [5]. Patient education is vital if dyspnea
crises are present, and should encompass breathing training, an action plan, and individualized use of a fan, amongst others [6].

In recent years, evidence-based multidisciplinary holistic breathlessness services have been developed, mostly emerging from palliative care services in the UK and Germany [7–12]. Higginson et al. [10], in a study involving predominantly patients with advanced nonmalignant diseases such as COPD, heart failure, interstitial lung disease and motor neuron disease, found a significant and clinically relevant improvement in breathlessness mastery. However, evidence for the impact on mastery in people with nonmalignant disease is not consistent: a German randomized controlled trial (including patients with COPD, motor neuron disease, pulmonary hypertension, heart failure and interstitial lung disease, as well as cancer) found that mastery improved significantly, but did not reach the minimum clinically important difference [11]. A Cambridge trial, involving only patients with nonmalignant disease, had a positive qualitatively identified impact, but there was no significant improvement in distress due to breathlessness [12]. More recently, a Canadian breathlessness service retrospectively assessed its effectiveness for COP D patients and found no difference in breathlessness before and after the enrollment, although there was some benefit for almost half of the patients [13].

Breathlessness services have not been universally adopted in all countries. Apart from the reason that the effects in trials have not been unequivocal, this may be due to the sporadic availability of ambulatory palliative care services, particularly for people with nonmalignant disease[14,15].
Consequently. there is a concerning gap in the care for patients with COP D and refractory breathlessness. Indeed, patients with COP D who refrain from pulmonary rehabilitation and do not visit a dedicated physiotherapist are likely to miss out on individualized breathlessness management support[16].

The goal of the current study was to investigate whether it is feasible to set up a breathlessness service specifically for COP D patients, in a respiratory outpatient setting and without involvement of anexpert palliative care team.

METHODS

Study design

We conducted a prospective, single-center non-blinded feasibility study. The predefined criterion for assessing feasibility was 75% of the included patients completing the intervention. Secondary objectives were:

A assessing how many sessions patients needed to complete the intervention.

B obtaining an indication of effect size, using a Dutch translation of the Chronic Respiratory Questionnaire (CRQ). The CRQ is an interviewer led questionnaire and scores 20 items across 4 domains: dyspnea (5 items), fatigue (4 items), emotional functioning (7 items) and mastery (4 items). The mastery domain was appointed as the most relevant domain for this study, since it reflects the subjects' feeling of control over the disease, as well as the impact the disease has on quality of life. Scale range is 1-7; high values indicate low burden. The minimum clinically important difference is 0.5[17].

C assessing patient satisfaction with a designed-for-purpose questionnaire. (See the measurements paragraph.)

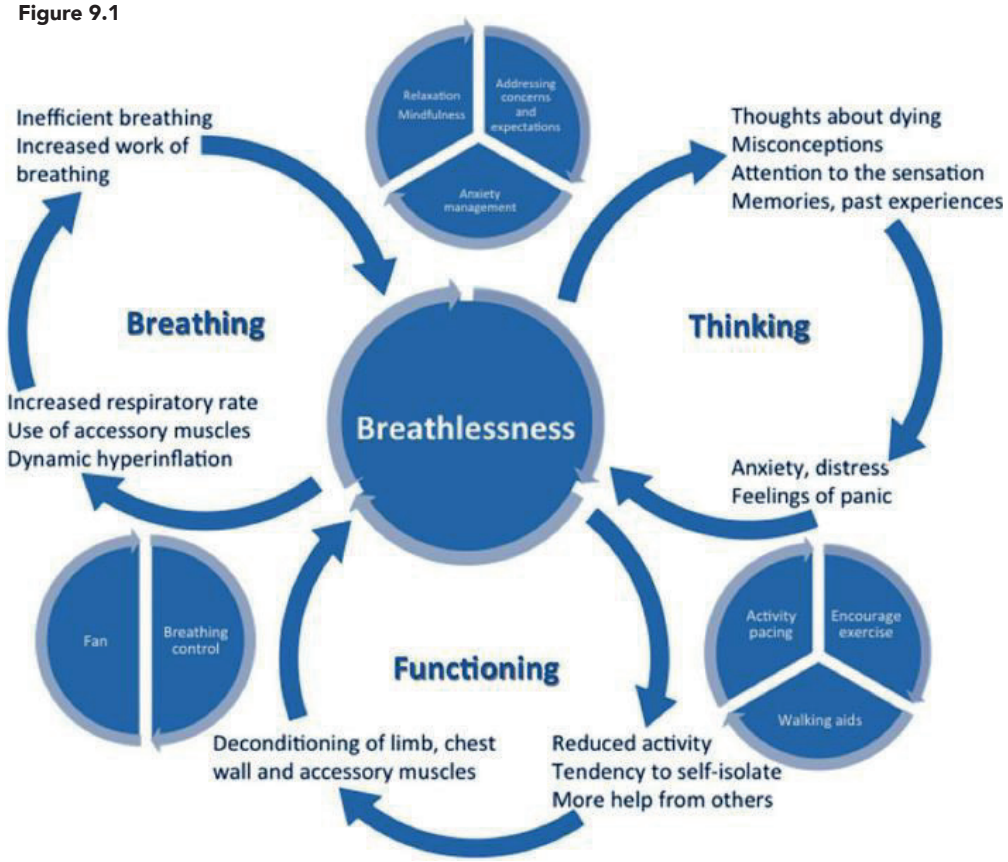
Subjects and screening

Outpatients with COP D (diagnosed by a pulmonologist, post-bronchodilatator FEV_1/FVC below the lower limit of normal) were eligible for the study if they reported refractory dyspnea (troubled by breathlessness despite optimization of COP D treatment) with a Medical Research Council (MRC)dyspnea score of three or higher. Exclusion criteria were cognitive impairment and inability to speak Dutch. Patients were recruited by their treating pulmonologists and respiratory nurses. If patients agreed to receive information about the study, they received a letter with study information and were called by one of the investigators at least one week later.

Intervention

We collaborated with a well-established service, the Cambridge Breathlessness Intervention Service (CBIS), to learn components of service, and how to deliver them. CBIS has developed the breathingthinking-functioning model (BTF), an educational tool for health professionals caring for breathless people, that is increasingly used in practice with breathless patients[18]. This model increases understanding of cognitive and behavioral reactions to breathlessness that may worsen and maintain the symptom (Figure 9.1). The aim of the intervention is to break the key vicious cycle(s), with elements of cognitive behavioral therapy (challenging misconceptions a patient may have) as well as a "toolkit" of non-pharmacological techniques. Aided by this toolkit, patient and health care provider(s) make an individual breathlessness management plan. The BTF model was used to underpin our service, called Ademen Denken Doen (ADD) in Dutch. Key elements of ADD were copied and translated from the Cambridge Breathlessness Intervention Service (CBIS). The ADD service encompasses the following:

Figure 9.1



A Explanation of the interaction between 'breathing', 'thinking' and 'functioning'.

B Structured patient education on COPD.

C Challenging misconceptions the patient may have.

D Breathing techniques.

E Relaxation techniques.

F Physiotherapy session, opportunity to practise breathing techniques during exercise, opportunity to walk with a rollator.

The service uses a booklet in which key aspects of A, B, and D are explained and visualized (added as a supplement, in Dutch). For a more detailed description of intervention techniques per domain, see Tables 9.1- 9.3.

Table 9.1

Technique	Patient instruction	Mechanism
Breathe a rectangle	• Find a comfortable position • Look around for a rectangle (e.g. a door or a window) • Follow the sides of the rectangle with your eyes as you breathe, breathing in on the short sides and out on the long sides • Gradually slow the speed, pausing at the corners	• Reduction of hyperinflation by prolongation of the exhalation • Distraction
Hand-held fan	• Find a comfortable position • Direct airstream to the lower half of the face • Move fan from left to right at a comfortable distance from the face (handbreadth or more)	• Stimulating upper airway "flow" receptors and/or trigeminal skin receptors • Distraction • Relaxation
Focus on exhalation	• When you are breathless, it feels like you need more air; but instead, you need to make room for the next inhalation • Focus on outbreath, inbreath will take care of itself • 'Blow as you go': during exercise such as walking stairs, breathe out during exerting	• Reduction of (dynamic) hyperinflation
Belly breathing	• The lungs are shaped like cones: they are small in the top and large in the bottom • Don't put too much effort in moving the upper part (shoulders)	• Preventing dead space ventilation and exhaustion • Preventing hyperinflation • Relaxation by lowering shoulders
Pursed lip breathing	• Breathe in as if you smell a rose • Breathe out as if you want to make a candle flame flicker but not blow it out	• Preventing hyperinflation

Table 9.2 Thinking domain

Possible misconception	Explanation
One day I will suffocate	• The airways will never get completely blocked • However breathless you are, air will still move through the airways
I need (more) oxygen	• Your breathlessness is mostly related to the movement of air through the lungs, not so much to oxygen
I need to avoid feeling breathless	• Choosing to make yourself feel moderately breathless is not harming you; instead, it builds up fitness in your muscles • let's try to write down an action plan to prepare yourself for next time you feel breathless (e.g. "I can do this; I have had this before and it will go away; I will lean forward, use my fan").

Table 9.3 Functioning domain

Possible misconception	Explanation
Individualized plan for daily activities	• you have 40% of the lung capacity you had when you were healthy. It makes sense to say you can do 40% of the activities that you used to do • what gives you energy, what exhausts you?
Energy conservation strategies	• pacing instead of 'all or nothing' (boom and bust) • planning, prioritizing
Explanation of the function of a walking aid	• comparison with walking behind a shopping cart, which is often easier due to forward leaning and pacing

Unlike CBIS which sits within a palliative care service, ADD is delivered by a pulmonologist, a respiratory nurse and a physiotherapist. The pulmonologist received two days' training from CBIS, and subsequently trained the nurse and the physiotherapist.

ADD is a brief intervention: patients have at least one session with a pulmonologist and a respiratory nurse (combined), and one session with a physiotherapist who practiced the breathing techniques with them. The patients receive the booklet (with verbal explanation) and a hand-held fan (with instruction). If necessary, extra sessions are scheduled. Since there was no team experience with giving the intervention, the number of sessions for the feasibility trial was not fixed.

Measurements

- At baseline, all participating patients completed the CRQ. The CRQ was repeated during the last visit.
- Baseline characteristics such as pulmonary function tests were taken from the patient's medical file.
- The total number of visits to the outpatient clinic was reported.
- A designed-for-purpose postal survey was sent after the intervention. The survey consisted of 12 multiple choice questions regarding components of service (e.g. "Did you find the consultation with the physiotherapist helpful?", answer "yes/a little bit/no" with room for clarification). The postal survey was only sent once.
- After the pilot study, an evaluation meeting between the team members was held, and team members' feedback was documented.

Data analyses and statistics

We estimated that inclusion of 20 patients would be sufficient to answer our research questions. This sample size was deemed appropriate for testing acceptability of the intervention, to estimate how many sessions were needed to obtain an indication of the effect size on the CRQ (mastery domain) and to gather feedback from patients and health care providers on the strengths and weaknesses of the intervention. Because of the small sample size, only descriptive statistics were used.

Ethics, consent and permissions

Ethical approval was given by the Medical Ethics Review Committee of the Amsterdam University Medical Center (registration number 2019.199). All participating patients gave written informed consent. The trial was registered in the ISRCT N trial register, reference number: ISRCT N48274234.

RESULTS

Patient characteristics

34 Patients were screened for the study and received study information. Of those, five patients did not meet the inclusion criteria (four in terminal phase of COP D and therefore no longer able to visit the outpatient clinic, one with severe cognitive impairment). Three patients did not want to come to the hospital, and seven refrained from participating due to other personal reasons. Consequently, 19 patients were included in the study over a 13-month period (between October 2019 and November 2020). Patients were referred by a range of pulmonologists and respiratory nurses. Baseline characteristics of the study participants are shown in Table 9.4. All included patients were white and born in the Netherlands.

Table 9.4 Baseline Characteristics

Age (years)	67 (SD 6.9)
Men 6	6 (32%)
Women 13	13 (68%)
FEV1 (L)	0.93 (SD 0.2)
FEV1 (% predicted of GLI-12 reference values)	38 (SD 11)
FEV1/FVC	38 (SD (10)
Long term oxygen treatment 7	7 (37%)

Onder de table: SD: standard deviation.

Findings

All 19 recruited patients completed the intervention. They had a median of two visits to the outpatient clinic (SD 1.07) and two telephone calls by one of the team members (SD 1.74). The mean improvement in the mastery domain of the CRQ was 1.55; 17/19 patients improved by more than the MCID of 0.5. Mean CRQ scores also improved on the other three domains (see Table 9.5). Only 8/19 returned the patients satisfaction survey after the intervention. All respondents rated the service as excellent and helpful. Most patients found the 'breathing a rectangle' (see Table 9.1) the most useful breathing technique and were enthusiastic about the hand-held fan.

Table 9.5 Effects on CRQ

	Baseline, mean (n = 19)	**After intervention, mean (n = 19)**	**Number of patients with change in score of ≥ 0.5**
CRQ dyspnea (score range 1–7)	2.18 (SD 0.83)	3.95 (SD 1.10)	15 (79%)
CRQ emotion (score range 1–7)	3.57 (SD 1.26)	5.04 (SD 0.99)	16 (84%)
CRQ fatigue (score range 1–7)	2.87 (SD 1.32)	4.42 (SD 1.47)	14 (74%)
CRQ mastery (score range 1–7)	3.67 (SD 1.6)	5.22 (SD 1.16)	17 (89%)

Implementation of the intervention within the team was relatively easy. During the evaluation meeting, the team members all described the BT F model as very helpful in both the exploration and the management of refractory breathlessness. They considered that delivering the service had raised their awareness of the symptom and given them more insights into its management. Furthermore, other colleagues were enthusiastic about the option to refer to the service, and stated that it made them more aware of refractory breathlessness, increased their knowledge on breathlessness management and increased their willingness to speak about breathlessness with their patients. Handheld fans were made available for breathless patients both in the outpatient clinic and on the ward.

DISCUSSION

ADD has shown potential as a breathlessness service for patients with COP D. The service is delivered by a pulmonologist, a respiratory nurse and a physiotherapist, making it theoretically possible to implement this service in any pulmonary outpatient clinic.
It is a brief intervention: most patients reached better symptom control after two to three sessions and two telephone calls. Recruitment for this feasibility trial was relatively easy, the service was well-received and all included patients completed the study.

Almost all patients (17 out of 19) experienced an improvement in breathlessness mastery as measured with CRQ. Although our trial was not designed to measure effectiveness, it is interesting to consider why the results may be more positive than in four previous studies focused on people with nonmalignant disease[10–13]. First, patients received the service within their own outpatient clinic, from members of their usual care team. It is possible that patients prefer to learn breathlessness management strategies from their familiar healthcare team, instead of a palliative care team. Indeed, patients may have misconceptions on the word 'palliative' (which is often associated with the end of life)[16].
Second, our patients' baseline knowledge on breathlessness management may have been lower than in the other studies. For instance, none of our patients were familiar with the use of a handheld fan, which may have been different in the UK or German study populations. Third, this is the first study to date using the BT F model to underpin the clinical intervention and it is possible this contributed to the positive findings. For example, the 'breathing a rectangle'- exercise, which our patients found quite helpful, is not widely used in other breathlessness services to our knowledge.
Fourth, previous studies included people with a wide range of respiratory nonmalignant conditions, whereas ADD was aimed only at people with COPD; it could be argued that COP D patients are particularly likely to benefit, as presence of hyperinflation, along with associated maladaptive breathing patterns, makes them more amenable to benefit from breathing techniques than those with conditions with restrictive pathology and/or low diffusion capacity[19]. Furthermore, many patients with advanced COPD experience unpredictable (untriggered) episodic breathlessness, more so than in other patient groups, which the ADD explicitly sought to manage[4].

A properly powered randomized controlled trial is needed to determine whether breathlessness services embedded within respiratory care are indeed effective and also cost-effective. ADD delivers non-pharmacological breathlessness management strategies that should be offered to all COPD patients with refractory breathlessness[5,6,14]. However, such breathlessness management strategies are not widely available to the many patients who - for various reasons such as fatigue, anxiety, transportation difficulties, limited privacy and avoiding confrontation with severely ill patients – decline pulmonary rehabilitation[20]. Furthermore, health insurers must agree to reimburse the extra time it takes to deliver such a symptom-focused service. Setting up a multicenter randomized controlled trial would be helpful in increasing availability of a breathlessness service for COPD patients.

Strengths

The tested intervention builds on an existing model for non-pharmacological breathlessness management (BT F), for which research data are still scarce. We showed that the intervention was easily transposed into an outpatient setting. This intervention can be given in clinics in which a palliative care team is not yet available for outpatients.
The high patient adherence is promising. It is a low-cost intervention, which has the potential to improve quality of life in patients and raise awareness of the breathlessness problem in health care providers.

Limitations

Our study has important limitations. The positive effects we found in this population should be interpreted with caution. There was no control group and the marked positive change in CRQ might partly be due to a Hawthorne effect. The fact that the service was delivered and evaluated by the team members that treated the patients' COPD is a potential source of bias. Furthermore, only 42% of participants returned the postal survey to give feedback on the intervention, which may be partly due to low literacy skills. (In the Netherlands, almost half of COP D patients have low health literacy[21].
Those who returned the questionnaire rated all parts of the intervention as 'excellent' without any other comments. Since 17 out of 19 patients responded to the intervention, a response bias is less likely, but the low response rate limits the validity of this result.
In hindsight, qualitative interviews with participants would have provided much better insight in their experience of this intervention.

Furthermore, we did not measure how long the positive effects on breathlessness mastery lasted.
Finally, the intervention was delivered in a single center only.

CONCLUSION

Delivering a breathlessness service, without involvement of a palliative care team, was feasible in patients with COP D in a single-center respiratory out-patient setting. Intervention adherence was high, both patient and professional participants were enthusiastic about the service, and patients' CRQ scores improved markedly. This study suggests that it would be feasible and worthwhile to undertake a large randomized multicenter controlled clinical trial to test clinical and cost-effectiveness of such a service.

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Summary and genaral discussion

SUMMARY

The aim of this thesis was gathering knowledge on how to improve care for patients with advanced COPD, given on a respiratory outpatient clinic. The research questions arose from our daily practice. The studies that are part of this thesis are summarized below.

Few patients suffering from advanced COPD are referred for palliative care. One of the barriers for referral is lack of consensus on which patients are eligible for a palliative approach. Existing tools to identify patients are cumbersome to apply in daily practice. **In chapter 2,** we hypothesize that after hospitalization for COPD, the 'surprise question' (SQ) ("Would I be surprised if this patient dies within 12 months?") may be used as a screening tool to identify patients in need of palliative care. To test specificity and sensitivity of our tool, we used the so-called Gold Standard Framework Prognostic Indicator Guidance as a gold standard test. We concluded that the SQ after recent hospitalization for COPD has a very high specificity compared to a standardized tool. It is therefore a useful tool for the quick identification of patients who are most likely to benefit from palliative care. However, this method doesn't identify all patients who are eligible for referral to palliative care.

Oxygen is commonly prescribed to patients with severe COPD. However, little is known about the perspectives COPD patients, who do not yet use oxygen, have on this treatment. **In part 2, chapter 3,** we describe the results of in-depth interviews with oxygen-naïve patients with advanced COPD. We found that the message that home oxygen should be started, has a huge negative impact on most patients. The rationale behind the therapy and the way it is delivered are not widely known. Misconceptions such as tank explosions, becoming housebound, full dependency on oxygen and an imminent death are common. Furthermore, many patients anticipate social isolation and smoking-related stigma. This may be related to the fact that oxygen makes their disease visible, which is in conflict with the urge to hide it. **In chapter 4,** the topic of smoking-related stigma is further explored, but from the physician's perspective. We explored pulmonologists' attitudes towards smoking COPD patients in a qualitative study. All participants said patients are not fully responsible for their smoking behaviour. Contrarily, smoking was also seen as a free choice by most physicians. Moreover, smoking cessation was mostly seen as the responsibility of the patient. Feelings of powerlessness, frustration and compassion were reported in the guidance of patients with COPD.

The cardinal, debilitating symptom of advanced COPD is breathlessness, which persists in most patients, even when disease management has been optimized. **Part 3** concerns with the pharmacological option of morphine. In 2015, when the first study of this thesis was written **(chapter 5)**, it was assumed that morphine was effective in the management of refractory breathlessness. We explored the attitudes of Dutch chest physicians toward prescription of opioids for refractory breathlessness to outpatients with advanced COPD and to investigate the barriers for opioid prescription. We concluded that Dutch chest physicians (in training) rarely prescribed opioids for refractory breathlessness to outpatients with advanced COPD.
In 2021, when the next study in this thesis on opioids was published **(chapter 6)**, evidence for opioids for refractory breathlessness had turned out to be less robust than appreciated. A systematic literature search was performed, assessing placebo-controlled randomized clinical trials (RCT) investigating opioids for refractory dyspnea caused by COPD, with dyspnea, health status and/or quality of life (QoL) as endpoints. From this assessment of the literature, we found that even though opioids have found their way into COPD guidelines as a treatment option for refractory dyspnea, the evidence is still inconclusive. Furthermore, it is unknown what the effectiveness is of the opioid fentanyl. However, trials investigating short-acting fentanyl, suggest that it could give a reduction of breathlessness, possibly with less side effects compared to morphine. The design of a trial comparing morphine and fentanyl is described; we believe this study will provide valuable information on which patients are eligible for which opioid.

In part 4, we explore non-pharmacological options in breathlessness management. Since breathlessness provokes anxiety in many patients, and anxiety aggravates the symptom, we have explored therapies that may help them to master their anxiety. The first is cognitive behavioural therapy (CBT). In a literature review article **(chapter 7)**, we summarize specific CBT techniques that have been proven effective in COPD. We formulate the need for a Dutch treatment protocol that describes specific CBT techniques for COPD and that can be applied by practitioners who have experience with COPD, such as (pulmonary) nurses, respiratory physiotherapists and practice nurses. Furthermore, a specific psychological treatment for patients who have lived through breathlessness crises, leading to anxiety and fear of suffocation, is described in **chapter 8**. We hypothesized that these breathlessness crises are psychotraumatic events for some patients, and that they share characteristics with those who suffer from post-traumatic stress disorder (PTSD). In PTSD, eye movement desensitization and reprocessing (EMDR) is the therapy of choice. We explored the hypothesis that EMDR in patients with chronic obstructive pulmonary disease (COPD) and previous severe breathlessness episodes, improves breathlessness mastery by decreasing the anxiety component. Since we found no literature on previous research on this subject, we undertook a qualitative case series on four patients with COPD GOLD 4/D and refractory breathlessness. We found that all four patients improved with regard to breathlessness mastery. After the EMDR, all patients made a distinction between 'regular' breathlessness and breathlessness intertwined with anxiety.
We conclude the chapter with a study on the implementation of a breathlessness service in the Netherlands **(chapter 9)**. Symptom-focused breathlessness services, involving palliative care teams, offer individualized support but are not yet widely available for people with COPD. Our primary aim was to demonstrate the feasibility of setting up a breathlessness service specifically for COPD patients within a respiratory outpatient clinic. For this non-randomized single-center feasibility study, we included 19 patients with COPD and refractory breathlessness. During at least one session with a respiratory nurse and a pulmonologist, and one session with a physiotherapist, patients learned non-pharmacological interventions to manage their symptom. According to this pilot study, delivery of a breathlessness service for COPD outpatients appears feasible, easy to implement in a respiratory outpatient clinic, and has the potential to be effective. A randomized controlled clinical trial is needed to test effectiveness and cost-effectiveness in this context.

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift was onze kennis te vergroten over de zorg die we op de polikliniek longziekten geven aan mensen met ernstige chronisch obstructieve longziekte (COPD). De onderzoeksvragen kwamen voort uit onze dagelijkse praktijk. De onderzoeken in dit proefschrift worden hieronder samengevat.

Weinig patiënten met ernstig COPD worden doorverwezen voor palliatieve zorg. Een van de belemmeringen voor verwijzing is het gebrek aan consensus over welke patiënten in aanmerking komen voor deze zorg. Bestaande instrumenten om patiënten te identificeren zijn in de dagelijkse praktijk lastig toe te passen. In **hoofdstuk 2** onderzochten we de stelling dat na ziekenhuisopname voor COPD, de 'surprise question' (SQ) ("Zou het mij verbazen als deze patiënt binnen 12 maanden zou overlijden?") kan worden gebruikt als screeningsinstrument. Om de specificiteit en gevoeligheid van onze 'tool' te onderzoeken, hebben we de zogenaamde 'Gold Standard Framework Prognostic Indicator Guidance' als gouden standaard gebruikt. We concludeerden dat de SQ na recente ziekenhuisopname voor COPD een zeer hoge specificiteit heeft, in vergelijking met deze gestandaardiseerde tool. Het is daarom een handig hulpmiddel voor het snel identificeren van patiënten die zeker baat zullen hebben bij palliatieve zorg. Deze methode identificeert echter niet alle patiënten die in aanmerking komen voor palliatieve zorg.

Zuurstof wordt vaak voorgeschreven aan patiënten met ernstig COPD. Er is echter weinig bekend over de ideeën en aannames die patiënten, die nog geen zuurstof gebruiken, over deze behandeling hebben. In **hoofdstuk 3** beschrijven we de resultaten van diepte-interviews met zuurstof-naïeve patiënten met vergevorderd COPD. We ontdekten dat de boodschap, dat er gestart moet worden met zuurstof thuis, een enorme negatieve impact heeft op de meeste patiënten. De rationale achter de therapie en de manier waarop deze wordt toegediend, is niet algemeen bekend. Misvattingen als tankexplosies, aan huis gekluisterd raken, volledige afhankelijkheid van zuurstof en overlijden op korte termijn komen vaak voor. Bovendien vrezen veel patiënten een sociaal isolement en aan roken gerelateerd stigma. Dit kan te maken hebben met het feit dat zuurstof hun ziekte zichtbaar maakt, wat in strijd is met hun neiging om deze te verstoppen.
In **hoofdstuk 4** wordt het onderwerp rookgerelateerd stigma verder uitgediept, maar dan vanuit het perspectief van de arts. We onderzochten de houding van longartsen ten opzichte van rokende COPD-patiënten in een kwalitatief onderzoek. Alle deelnemers zeiden dat patiënten niet volledig verantwoordelijk zijn voor hun rookgedrag. Tegelijkertijd werd roken ook gezien als een vrije keuze. Bovendien werd stoppen met roken vooral gezien als de verantwoordelijkheid van de patiënt. De begeleiding van mensen met COPD en een rookverslaving kan gevoelens oproepen van machteloosheid, frustratie en medeleven.

Het belangrijkste symptoom van vergevorderde COPD is kortademigheid. Ondanks optimale behandeling houden de meeste patiënten hier last van. **Deel 3** gaat over de farmacologische optie van morfine. In 2015, toen de eerste studie van dit proefschrift werd geschreven **(hoofdstuk 5)**, werd aangenomen dat morfine effectief was bij de behandeling van refractaire kortademigheid. We onderzochten de houding van Nederlandse longartsen ten aanzien van het voorschrijven van opioïden voor refractaire kortademigheid aan poliklinische patiënten met vergevorderd COPD. Welke barrières om opioïden voor te schrijven leven er? We concludeerden dat Nederlandse longartsen (in opleiding) zelden opioïden voor refractaire kortademigheid voorschreven aan poliklinische patiënten met vergevorderde COPD. In 2021, toen de volgende studie in dit proefschrift over opioïden werd gepubliceerd **(hoofdstuk 6)**, bleek het bewijs voor opioïden voor refractaire kortademigheid minder sterk dan eerder werd aangenomen. Er werd een systematisch literatuuronderzoek uitgevoerd. Hierbij werden placebogecontroleerde gerandomiseerde klinische onderzoeken (RCT's) beoordeeld, waarin opioïden werden gegeven voor kortademigheid door COPD. De studies hadden kortademigheid, gezondheidsstatus en/of kwaliteit van leven als eindpunten. Uit dit literatuuronderzoek concludeerden we dat hoewel opioïden een plaats hebben gekregen in COPD-richtlijnen als optie voor refractaire kortademigheid, het bewijs nog steeds niet doorslaggevend is. Verder is niet bekend wat de effectiviteit is van het opioïd fentanyl. Studies waarin kortwerkend fentanyl werd onderzocht, suggereren dat het een afname van kortademigheid zou kunnen geven, mogelijk met minder bijwerkingen dan morfine. Het design van een studie waarin morfine en fentanyl worden vergeleken, wordt beschreven; wij verwachten dat deze studie waardevolle informatie zal opleveren over welke patiënten in aanmerking komen voor welke opioïden.

In **deel 4** verkennen we niet-medicamenteuze opties voor de behandeling van kortademigheid. Omdat kortademigheid bij veel patiënten angst veroorzaakt en angst het symptoom verergert, hebben we therapieën onderzocht die hen kunnen helpen de angst onder controle te krijgen. De eerste is cognitieve gedragstherapie (CGT). In **hoofdstuk 7** vatten we specifieke CBT-technieken samen, waarvan bewezen is dat ze effectief zijn bij COPD. We benoemen de noodzaak voor een Nederlands behandelprotocol voor CGT bij COPD, dat kan worden toegepast door o.a. (long)verpleegkundigen, longfysiotherapeuten en praktijkondersteuners.
Verder wordt in **hoofdstuk 8** een specifieke psychologische behandeling beschreven voor patiënten die een kortademigheidscrisis hebben meegemaakt, die tot stikangst heeft geleid. Onze hypothese was dat deze kortademigheidscrises psychotraumatische gebeurtenissen kunnen zijn. We denken dat patiënten met COPD, die deze crises doorgemaakt hebben, overeenkomsten vertonen met mensen die lijden aan een posttraumatische stressstoornis (PTSS). Bij PTSS is Eye Movement Desensitization and Reprocessing (EMDR) de voorkeurstherapie. We onderzochten de hypothese dat door EMDR de ervaring van kortademigheid minder hevig wordt, doordat de angstcomponent afneemt. Omdat we geen eerder onderzoek over dit onderwerp konden vinden, hebben we een kwalitatieve 'case series' uitgevoerd bij vier patiënten met COPD GOLD 4/D en refractaire kortademigheid. We ontdekten dat alle vier de patiënten beter met hun kortademigheid overweg konden na de EMDR. Na de EMDR maakten alle patiënten onderscheid tussen 'gewone' kortademigheid en 'paniek'-kortademigheid.
We sluiten **deel 4** af met een onderzoek naar de implementatie van een 'breathlessness service' in Nederland **(hoofdstuk 9)**. Symptoomgerichte interventies voor kortademigheid, georganiseerd door palliatieve teams, bieden geïndividualiseerde ondersteuning. Deze interventies zijn in Nederland nog niet beschikbaar voor mensen met COPD. Ons

primaire doel was om de haalbaarheid aan te tonen van een 'breathlessness service' specifiek voor COPD-patiënten binnen een respiratoire polikliniek. Voor deze niet-gerandomiseerde single-center pilotstudie includeerden we 19 patiënten met COPD en refractaire kortademigheid. Tijdens ten minste één sessie met een longverpleegkundige en een longarts, en één sessie met een fysiotherapeut, leerden patiënten niet-medicamenteuze interventies om met hun symptoom om te gaan. Volgens deze pilotstudie is het aanbieden van een kortademigheidsdienst voor poliklinische COPD-patiënten haalbaar, eenvoudig te implementeren op een polikliniek longziekten en zou het effectief kunnen zijn. Een RCT is nodig om de effectiviteit en kosteneffectiviteit in deze context te onderzoeken.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

INTRODUCTION

This thesis focusses on care for patients with advanced COPD, given in a respiratory outpatient clinic. Although our research questions were quite diverse, the common denominator was: how can we improve this care? Within this broadly formulated aim, the following sub-questions were addressed:

1 Which patients with COPD are eligible for palliative care?
2 What perspectives do patients with COPD have on starting home oxygen therapy?
3 How do pulmonologists regard patients with COPD who smoke?
4 To what extent are pulmonologists willing to prescribe opioids to breathless patients with COPD, and what is its evidence in the management of refractory breathlessness?
5 Are cognitive behavioral therapy (CBT) and eye movement desensitizing and reprocessing (EMDR) beneficial for breathless patients with COPD?
6 Is it feasible to implement a multidisciplinary breathlessness service in a respiratory outpatient clinic?

Point by point, I will discuss whether our research questions have been answered. I will analyze our findings, compare them to the existing literature, comment on their relevance for our daily practice and make recommendations for future research.

IDENTIFICATION OF COPD PATIENTS ELIGIBLE FOR PALLIATIVE CARE

This study (chapter 2) arose from the question that has held clinicians, caring for patients with COPD, busy for many years: which patients with COPD should be referred to palliative care services, and when? Despite a high symptom burden and a poor prognosis, patients with severe COPD are infrequently referred to such services. We postulated that referral was hindered by the fact that existing tools to identify those in need of palliative care, are unpractical to use. We assumed it would be helpful to be able to swiftly identify those who were evidently eligible.
The simple tool we developed, combining a negative answer to the surprise question ("No, I would not be surprised if this patient were to die in the following year") in combination with at least one hospitalization for COPD in the last year, was indeed able to identify the 'tip of the iceberg' group of patients (those for whom palliative care is most needed).
The question which COPD patients to refer (and when) is still largely unanswered. Although another identification tool has been developed in the Netherlands [1], its use is not advised in our national guideline on palliative care for patients with COPD [2].
Possibly, the problem with identification tools for palliative COPD care is that they rely on two shaky assumptions:

1 In COPD, there is some transition point, after which a patient has a poor prognosis and is in the 'palliative phase'.
2 A patient with COPD in the 'palliative phase' benefits from a change in the care that has been provided until that transition point.

As for the first assumption: The disease trajectory of COPD is usually long, with a very slow decline and unpredictable, dangerous exacerbations. The prognosis of the disease is unclear and there is no clear transition point to a palliative phase [3]. There are, however,

several 'milestones' (such as the first hospitalization for an exacerbation, or the start of home oxygen) that are significant within the disease trajectory [4].
The second assumption seems more obvious. However, a recent systematic review on palliative care interventions for patients with COPD found mixed and inconclusive results on effectiveness [5]. Indeed, six out of seven studies found no positive effect on quality of life. Of note, in lung oncology, the effectiveness of referral to a palliative care team is indeed proven [6].
In the same review by Broese *et al.*, qualitative data implied that education on breathlessness management, direct access to a professional for support and an ongoing relationship are pivotal for COPD patients. In other words, patients appear to prefer (a modification of) their regular COPD care to a palliative care service. There are at least two reasons why this may indeed be the best way to go.
First, the symptoms COPD patients experience require extensive knowledge of COPD and its therapy. There is usually no clear distinction between therapy directed at the disease and symptom control. (Bronchodilators, oxygen and non-invasive ventilation may all relieve breathlessness, but are generally not considered palliative interventions.) The respiratory team has expert knowledge on these interventions and is therefore best equipped to support these patients. The provision of advance care planning, which is an essential element of palliative care, should be intertwined with evaluating therapeutic interventions. ("You were ventilated with a mask during your last hospital admission. How do you look back at it? Would you want it again in the future?")
Second, even though their quality of life is low and their prognosis often poor, many patients accept their situation as a way of life rather than an illness [7]. A sudden transition to palliative care has little resonance with these patients.
In conclusion, we should probably stop looking for identification tools and transition points. We don't need them if we integrate palliative care within existing COPD care pathways. This integration challenges us to further develop the psychosocial aspects of care, amongst others.

PERSPECTIVES OF COPD PATIENTS ON STARTING HOME OXYGEN THERAPY, AND PERSPECTIVES OF PULMONOLOGISTS ON SMOKING

Many healthcare professionals who work in respiratory care have noticed how strongly patients may react to the message that they are eligible for home oxygen. The results of our qualitative study (chapter 3) on this subject are illustrative of how patients' perspective may differ from those of healthcare providers. Healthcare providers see therapeutic benefits, such as a more favorable prognosis, less breathlessness and better quality of life [8]. Although many patients have the same views, the majority of interviewees in our study had misconceptions, such as tank explosions, becoming housebound and isolated from society, full dependency on oxygen and an imminent death. Although our study population was too small to draw conclusions in this regard, misconceptions appeared to be more prevalent in those with lower health literacy. Healthcare professionals should be aware of these misconceptions, especially in 'vulnerable' patients. Actively addressing them might have a positive effect on anxiety and compliance. Together with the Lung Foundation Netherlands, we are working on a (digital) patient leaflet based on our findings. We hope this "Facts and myths on home oxygen" leaflet will be useful in this regard.

Moreover, the theme of smoking-related stigma became apparent from this study. Home oxygen suddenly makes a relatively invisible illness visible. The invisibility of COPD and breathlessness has previously been described [9,10]. Many patients experience feelings of shame, guilt and self-blame. Consequently, they often try to keep their breathlessness hidden from others, since it is evidence of a past of heavy smoking.
There is little research on shame and stigma in healthcare, and it receives little attention within the education curriculum of healthcare professionals working in respiratory care. Our study emphasizes that addressing stigma is a key element in communicating with COPD patients.

In order to promote awareness on this subject, we also undertook a qualitative study on the perspectives of pulmonologists on COPD patients who smoke (chapter 4). Understanding the doctor's view is equally important if we want to diminish feelings of stigma in patients. Do we contribute to these feelings, or do we actively try to take them away? Apparently, both. Many pulmonologists on the one hand consider smoking a free choice and hold patients responsible for cessation, whilst on the other hand they acknowledge the addictive nature of tobacco smoking. We recognize feelings of blame and shame in their patients but do not always act upon them.
To improve care with regard to stigma, we probably do not need more research, since all literature points in the same direction. We know stigma is highly prevalent in patients who suffer from a disease that bears a relationship with smoking, and healthcare providers should put more effort in diminishing stigma. The Dutch guideline on palliative care for patients with COPD acknowledges the importance of stigma and gives practical advice on how to address it (2). Examples of sentences that are helpful are:

- 'Many patients with COPD feel guilty because they have smoked. How is that for you?'
- 'I understand that you are angry with yourself for having smoked. However, I have a different opinion. I feel angry with the tobacco industry, that has made cigarettes extremely addictive, so that quitting is extremely difficult for most people.'

TO WHAT EXTENT ARE PULMONOLOGISTS WILLING TO PRESCRIBE OPIOIDS TO BREATHLESS COPD PATIENTS, AND WHAT IS ITS EVIDENCE IN THE MANAGEMENT OF REFRACTORY BREATHLESSNESS?

Our survey on the willingness of pulmonologists to prescribe opioids to COPD patients (chapter 5), dates from the period when we were convinced that opioids were effective in breathlessness management. Of note, opioids had already been adapted in national and international guidelines, while the level of evidence was still low to very low. In 2020, three randomized clinical trials on opioids (both morphine and oxycodone) were published [11,12,13]. According to these trials, summarized in chapter 6, opioids may give a small improvement in breathlessness in a limited number of patients with COPD. Although we are still curious for the potential role of fentanyl, the current body of evidence does not support the widespread prescription of opioids in COPD. Instead, a highly selective, careful approach is warranted. Opioids are not 'the answer' to the multifaceted and debilitating symptom that breathlessness really is. Rather, they are a tool within a toolkit that should encompass a range of non-pharmacological and pharmacological interventions.

Our previous focus on opioids may be regarded as an example of 'solution jumping': providing an answer before truly understanding the problem. Healthcare providers, and pulmonologists not in the least, are trained to be problem solvers. For many years, the issue of breathlessness in COPD did not receive a lot of attention - perhaps partly because we thought there was not really a solution. When a possible solution (morphine) presented itself, we embraced it rather too quickly. Nevertheless, current literature on breathlessness underscores the need for a multidisciplinary, individualized management plan, whbich reflects the complexity of the symptom. Non-pharmacological interventions may well be the most promising fore breathlessness management in the future.

ARE COGNITIVE BEHAVIORAL THERAPY (CBT) AND EYE MOVEMENT DESENSITIZING AND REPROCESSING (EMDR) BENEFICIAL FOR BREATHLESS COPD PATIENTS?

Speaking of non-pharmacological interventions, CBT is a promising tool in our breathlessness toolkit (chapter 7). CBT addresses misconceptions, for instance fear of suffocating[14]. If a patient suffers from fear of suffocating, the very thought of it alters the breathing pattern (more quick and shallow, leading to hyperinflation), thus aggravating the breathlessness. Assessing anxiety is not common practice for pulmonologists, who tend to focus on the somatic domain. Most pulmonologists know that anxiety is highly prevalent in COPD patients but tend to consider it a consequence of living with respiratory failure. However, it is more appropriate to regard anxiety as a key element of breathlessness, since it is often both a result and a 'driver' of breathlessness[15].
The important question is: whose responsibility is this psychological support? A close collaboration between a psychologist and the respiratory team is vital, ideally within multidisciplinary team meetings. This may promote referral to a psychologist or psychiatrist for eligible patients. However, not all patients want to be referred, and in-depth knowledge about COPD is limited within mental healthcare. Again, the respiratory team is probably best equipped for basic psychological support. Respiratory nurses, respiratory physiotherapists and practice nurses may all apply specific CBT techniques for COPD. The effectiveness of CBT in COPD, provided by a respiratory team, is a highly relevant topic for further research. Such a study would encompass designing a treatment protocol for CBT in COPD, which is an important step in promoting this support for our patients.

Another psychological intervention that warrants further study is EMDR (chapter 8). After EMDR, the four patients in our case series improved with regard to breathlessness mastery. They all made a distinction between 'regular' breathlessness and breathlessness intertwined with anxiety. The notion that a breathlessness crisis may lead to a post-traumatic stress syndrome in a subset of patients, underpins the tight relationship between breathlessness and the psyche. Interestingly, the idea for our case series on EMDR for refractory breathlessness in COPD came from patients. Whilst unknown in the medical literature, in practice this therapy is quite common in the Netherlands. Patients tell each other that it is helpful, and fortunately, they also told us. In breathlessness research, even more than in medical research in general, it is essential that we listen to patients' experiences. Indeed, we regard breathlessness differently than they do. There is a gap between symptom and experience, and between physiological disease and how it is lived by people[16]. Apparently, the approach of EMDR resonates with what matters to patients. The case series we performed should be the starting point of a randomized controlled clinical trial on effectiveness of EMDR in the subset of COPD patients with high levels of anxiety and traumatic breathlessness memories.

IS IT FEASIBLE TO IMPLEMENT A BREATHLESSNESS SERVICE IN A RESPIRATORY OUTPATIENT CLINIC?

Breathlessness services are a relatively new concept, known mostly in the UK where they have been developed. These services are initiated by palliative care teams and support patients with breathlessness, irrespective of the underlying disease.
To organize an effective breathlessness service in the Netherlands, where most palliative care teams do not (yet) organize outpatient services, we decided - again - to make the respiratory team responsible (chapter 9). According to the pilot study we undertook, a breathlessness service for COPD outpatients appears feasible, easy to implement in a respiratory outpatient clinic, and has the potential to be effective.
One might ask whether our model of care might still be called a breathlessness service. It is not initiated by palliative care anymore, it is for COPD only and you use your own respiratory team. Isn't it just a breathing training?
The answer is that our service is not 'usual care' for these patients. They receive at least two sessions that are fully dedicated to controlling breathlessness. Patients find the Breathing-Thinking-Functioning model, that underpins the service, very helpful. And after their session with the respiratory nurse, they go to the exercise room with the physiotherapist, to practice with the breathing techniques that they just learned. If the service of a psychologist or an occupational therapist is necessary, they are asked to see the patient separately. But perhaps the most helpful step for these patients is the fact that there is ample time and attention to their symptom. To learn that they are not the only patients who are struggling with breathlessness, and that there may be tips for coping with it. In our study, patients appreciated the fact that the service was delivered by team members they know and trust, who understand their disease.
On the other hand, in our hospital, delivering this service has also changed the way the respiratory team works. Elements of the service, such as the 'breathing a rectangle' technique and the handheld fan, are often recommended to patients. In other words, elements of the service may well diffuse with our daily practice. Just as "palliative care" and "advance care planning" are not always clearly demarcated within our COPD care. Is that problematic? On the contrary, I think it is the way to go. But it is essential that the respiratory team is adequately trained to deliver this supportive care, integrated within usual care. Investigating the effectiveness of our breathlessness service in a Dutch randomized controlled clinical trial, might be a good way to promote awareness of the symptom and train other teams in managing breathlessness.

METHODOLOGICAL CONSIDERATIONS

The present thesis had some important limitations that should be considered when interpreting the results. The sample size in chapter 3, on perspectives of oxygen-naïve COPD patients on long-term oxygen use is too small to draw firm conclusions. In chapter 4, on smoking behaviour and stigma, pulmonologists may have given socially desirable

answers, especially since the interviews were held in a period in which the problem around smoking and the tobacco industry received ample attention in the Dutch media.
Our survey among Dutch chest physicians on attitudes toward opioids for breathlessness in chapter 5 had a low response rate (22.5%). We do not know whether the attitudes we found are comparable with the attitudes of physicians who did not respond to our survey. Furthermore, non-responders were more likely to work in an academic setting than in the total Dutch population of pulmonologists and respiratory residents. For our consecutive case series (chapter 8, on EMDR), we were unable to include more than four patients. Those patients were included in a single centre, and reason for inclusion was that they asked for EMDR. The fact that they wanted EMDR (in most cases because they had heard from other patients that it was effective) might have introduced a bias.
Chapter 9, on the feasibility of a COPD-specific breathlessness service, had no control group and the marked positive change in CRQ might partly be due to a Hawthorne effect. The fact that the service was delivered and evaluated by the team members that treated the patients' COPD is a potential source of bias. Furthermore, only 42% of participants returned the postal survey to give feedback on the intervention, which may be partly due to low literacy skills. Finally, this intervention too was delivered in a single center only.

IMPLICATIONS FOR DAILY PRACTICE AND RECOMMENDATIONS FOR RESEARCH

We should attempt to intertwine palliative care with existing COPD care pathways. The respiratory team is primarily responsible for providing this care. Adequate training of this team should ideally encompass:

- Good communication skills, particularly regarding awareness of shame and stigma and how to respond to it
- Awareness of myths regarding home oxygen
- Non-pharmacological breathlessness management

With regard to research, we should investigate the effectiveness of CBT in COPD, provided by a respiratory team. The role of EMDR in patients with COPD and fear of suffocation should be explored further, by means of a randomized controlled clinical trial.
Lastly, respiratory outpatient clinics should offer a breathlessness management service for patients with COPD. Whether the intervention we used in chapter 9 is effective in improving the distress caused by breathlessness, should be investigated with a randomized multi-centre design.

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Appendices

DATA MANAGEMENT

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. Where applicable, ethical approval was granted by the Medical Ethics Review Committee of Amsterdam University, or the Committee confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply. This thesis was partly funded by a 'Principle Investigator Grant', awarded by the Spaarne Gasthuis in 2021.

The data for chapter 2 were extracted from the electronic health records system 'Epic'. Patient data were pseudonymised by using a code that was stored in a secured environment that is password protected. Patient data were analysed using Excel. The Excel dataset was stored separately from the pseudonymisation code in a secured environment, password protected. In the analysis dataset all identifiers except the pseudonymisation code were removed. Data will be stored for five years according to good clinical practice (GCP) guidelines and will be made available upon request.

For the qualitative studies in chapters 3, 4 and 8, audio-taped data were used. Transcripts were stored and analyzed in ATLAS.ti, version 9.1.3, licensed under Radboud Umc. This web-based program is password protected. The original data were stored in a secured environment, separately from the transcripts. All data were stored anonymously to maintain confidentiality. All data will be stored for five years according to good clinical practice (GCP) guidelines. Data will be made available upon request.

The data for chapter 9 were stored and analyzed in Research Manager, an electronic case report form, licenced under Spaarne Gasthuis. This web-based program generates a unique subject identification code, based on number of enrolment into the study, not on patient initials and/or date of birth. The data will be kept for 15 years. Research Manager fulfils all GCP standards for electronic data collection. Investigators who have access to Research Manager all have a unique password. Data will be made available upon request.

DANKWOORD

Als longartsen onderzoek doen naar COPD, ligt de focus meestal op de ziekte zelf, meer op 'cure' dan 'care'. We zijn getraind om problemen op te lossen, met veel kennis van de longen - en wat blinde vlekken voor de rest. Dus als je als longarts een proefschrift over palliatieve zorg bij COPD wil schrijven, is samenwerking met anderen essentieel. Graag wil ik hier mijn dank uitspreken aan alle inspirerende mensen die onmisbaar waren bij dit project.

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CURRICULUM VITAE KRIS MOOREN

Kris is geboren in 1976 in Heemstede, waar ze ook opgroeide. Ze haalde in 1994 haar gymnasiumdiploma aan lyceum Sancta Maria in Haarlem. Van 1995 tot 1999 studeerde ze voor haar doctoraal geneeskunde aan de Vrije Universiteit in Amsterdam. Ondanks een periode met twijfels over de te vervolgen weg (waarin ze werkte als barvrouw en DJ, lange reizen maakte en vaak in de kroeg zat) studeerde ze af in 2003. Na een jaar als artsassistent interne geneeskunde, longziekten en cardiologie te hebben gewerkt in het Kennemer Gasthuis (nu: Spaarne Gasthuis), werd ze in 2004 aangenomen voor de opleiding longziekten in het Onze Lieve Vrouwe Gasthuis in Amsterdam. Een deel van haar opleiding volbracht ze in het VU Medisch Centrum (nu: Amsterdam UMC) en in het Medisch Centrum Alkmaar (nu: Noordwest Ziekenhuisgroep). Tijdens haar opleiding was ze lid van het assistentenbestuur van de longartsenvereniging (NVALT). In 2010 was ze mede-oprichter van de Sectie Palliatieve Zorg van de NVALT, waarvan ze voorzitter is sinds 2016. Sinds 2013 is ze mede-organisator van de Clinic Palliative Care (nu: "Liverpool Goes Dutch"). In 2012 rondde ze haar opleiding tot longarts af en ging werken in het huidige Spaarne Gasthuis. In 2013 was ze hier één van de oprichters van het palliatief team van het ziekenhuis. In 2016 rondde ze de tweejarige kaderopleiding palliatieve zorg in Cardiff, Whales af. Ze schreef namens NVALT mee aan de richtlijn Palliatieve Zorg bij COPD (2020). Sinds 2021 is ze commissielid van ZonMw, subsidieronde Palliantie II. Kris en haar echtgenoot Damir Kalkan zijn de gelukkige ouders van zoon Imre (2008) en dochter Billie (2015).

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Education

1988-1994	grammar school, lyceum Sancta Maria, Haarlem
1994-1995	course in physics and chemistry, Free University, Amsterdam
1995-2003	Medicine, Free University, Amsterdam.
2014-2016	Postgraduate course Palliative Care, Cardiff University, UK

Work experience

2003-2004	resident internal medicine, Kennemer Gasthuis, Haarlem
2004-2009	resident pulmonology, Onze Lieve Vrouwe Gasthuis, Amsterdam
2005-2007	resident internal medicine, Spaarne Ziekenhuis, Hoofddorp

2009-2011	resident pulmonology, Medisch Centrum Alkmaar
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Januari 2012-heden	pulmonologist, Spaarne Gasthuis, Haarlem Member of palliative care team, Spaarne Gasthuis Haarlem

Other activities

2009 - 2011	Member junior board NVALT (Society of Dutch Pulmonologists)
2010 - now	Member and since 2016, Chairwoman Task force palliative care NVALT
2013 - now	Co-organizer Clinic Palliative Care in Liverpool (now: "Liverpool Goes Dutch")
2019 - 2021	Co-author Dutch guideline Palliative Care COPD
2021	Committee member ZonMw (Netherlands Organisation for Health Research and Development), project Palliantie II
2021 - now:	Member IKNL agenda committee guidelines palliative care
2022 (March-August)	Secretary 'Artsenhulp voor Oekraine'

List of publications

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