

Chronic breathlessness in COPD

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Scientific and social impact

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

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

Research and relevance

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

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



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

Target groups

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

Healthcare providers

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

Patients

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

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

Researchers

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

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

Activities and products

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

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

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



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