

# Management of refractory breathlessness in patients with advanced cancer

Steffen T. Simon<sup>1,2</sup> and Claudia Bausewein<sup>1,2</sup>

<sup>1</sup>Department of Palliative Care, Policy and Rehabilitation, King's College London, London, UK

<sup>2</sup>Institute of Palliative Care (ipac), Oldenburg, Germany

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## Behandlung der therapierefraktären Atemnot bei Patienten mit fortgeschrittenen Tumorerkrankungen

**Zusammenfassung.** Atemnot ist ein häufiges und belastendes Symptom bei Patienten mit fortgeschrittener Tumorerkrankung. Die Behandlung umfasst nicht-pharmakologische und pharmakologische Maßnahmen, die am besten miteinander kombiniert werden. Es gibt einige Evidenz überwiegend von Studien bei COPD-Patienten für den Einsatz von Rollatoren, neuro-elektrischer Nervenstimulation, Handventilatoren und Atemnotambulanz. Opioide sind die Medikamente der Wahl bei der Behandlung der Atemnot. Für den routinemäßigen Einsatz von Benzodiazepinen, anderen Anxiolytika, Antidepressiva, Phentiazinen, inhaliertem Furosemid und Sauerstoff gibt es derzeit keine ausreichende Evidenz.

**Schlüsselwörter:** Atemnot, Tumor, Palliativmedizin, Opioide, nicht-pharmakologische Interventionen

**Summary.** Breathlessness is a common and distressing symptom in advanced cancer. Management comprises non-pharmacological and pharmacological interventions, which are best combined. There is some evidence mainly derived from COPD studies for walking aids, neuro-muscular electrical stimulation, fan and breathlessness services. Opioids are the drugs of choice for pharmacological management of breathlessness. There is currently not enough evidence to support the routine use of benzodiazepines, other anxiolytics, antidepressants, phenothiazines, inhaled furosemide and oxygen.

**Key words:** Dyspnoea, cancer, palliative care, opioids, non-pharmacological interventions

## Introduction

Breathlessness is a distressing symptom towards the end of life for patients and carers, and is highly prevalent, occurring in up to 70% of patients with advanced cancer [1]. It is still one of the symptoms poorly understood and not managed satisfactorily [2]. A variety of treatment options are available that can be employed alone or in combination.

The first step to establish a treatment plan for a patient suffering from breathlessness is to make a clear diagnosis of the cause(s) of the symptom and to understand the impact of the symptom on the individual [3]. To assess the severity of breathlessness a unidimensional scale such as the visual analogue scale (VAS), the numerical rating scale (NRS) or the modified Borg scale seem to be most suitable [4]. The Cancer Dyspnoea Scale (CDS) defines dyspnoea from the patient's perspective including effort, anxiety and discomfort, and can also be used in the clinical setting as it is short and quick to complete [5]. A comprehensive physical examination will give indications for reversible problems such as pleural effusions or exacerbations of concurrent heart failure. Information from previous diagnostic tests will provide valuable information but occasionally an X-ray or ultrasound may give additional insights. Spirometry and oxygen saturation are widely used in the assessment of breathlessness but of limited value, as dyspnoea measures correlate at best moderately with pulmonary function [6, 7]. After initial assessment including physical examination and diagnostic tests, if necessary, treatment of reversible causes should be considered such as tapping of pleural effusions or optimising drug therapy for heart failure or airways obstruction. Breathlessness may be only defined as

Correspondence: Claudia Bausewein, Ph.D., M.D., M.Sc., Department of Palliative Care, Policy and Rehabilitation, King's College London, London SE5 9RJ, United Kingdom.  
 Fax: ++44-20-7848-5517, E-mail: claudia.bausewein@kcl.ac.uk

refractory when it persists despite maximal medical and other therapy of the underlying condition [8].

There are some general approaches when caring for a patient with breathlessness. Listening to patients' and carers' experience during breathlessness episodes is one of the most helpful strategies that a clinician can offer [9]. Patients also find an individualised 'breathlessness plan' helpful which is designed for and with them, incorporating pharmacological and non-pharmacological strategies [9]. Independent of the underlying illness, patients will often report that their breathing is more comfortable when sitting upright rather than lying flat which allows the rib cage to form a barrel shape providing better efficiency of the diaphragm and permitting the lungs to expand more [10]. Large meals may be burdensome for patients with breathlessness as there can be difficulty coordinating breathing and chewing. Therefore, many small energy dense meals spread throughout the day might decrease difficulty and avoid postprandial dyspnoea [10].

This review aims to summarise non-pharmacological and pharmacological treatment options for advanced cancer patients on the bases of the available evidence and also on what seems currently the most useful and effective therapies in the clinical setting.

## Non-pharmacological interventions

Non-pharmacological interventions play an important role in the management of breathlessness as drugs are often not as effective as hoped and because breathlessness has a big affective component in which emotions, personality, memory and expectations can also influence the patient's perception of breathlessness [11]. Any technique that the patients can initiate at a time of their choice and manage themselves promotes self-efficacy, which is associated with a reduced risk of depression and increased quality of life in patients with chronic illness [9].

A variety of non-pharmacological interventions are available for the management of breathlessness but most evidence is coming from studies in COPD patients and only few interventions have been tested in cancer patients [12]. Thus most evidence has to be extrapolated from COPD patients and further studies are necessary in cancer patients to confirm that interventions that are successful in COPD are also effective in cancer patients. In the following, interventions are discussed that have been tested in cancer patients or have shown to be effective in COPD patients and could easily be applied to cancer patients.

### *Breathlessness services*

Over the last ten years, a variety of breathlessness services have been developed to support cancer patients suffering from dyspnoea. Earlier services were provided by nurses offering counselling, breathing re-training, relaxation and teaching of coping and adaptive strategies [13, 14] or open access to nurse specialists with regular telephone assessments [15]. Two studies tested the combination of nurse-led counselling and support in combination with breathing and relaxation training to reduce breathlessness with weekly sessions for three to eight weeks. Both studies showed that breathlessness was reduced over time in the intervention but not in the control group [13, 14]. Open access to nurse specialists and regular follow-up and referral to medical team also led to a decrease in breathlessness in a patients with advanced cancer [15]. Services developed in more recent years were multiprofessional composed of doctors and physiotherapists and are offered to patients with intractable breathlessness from any disease with the aim to enhance the self-management of breathlessness [16, 17]. Interventions include evidence-based non-pharmacological interventions (psychological, social and physical), palliative care input (e.g. end-of-life issues, psychosocial issues, family concerns) and pharmacological review [17]. A formal evaluation of such a Breathlessness Intervention Service is currently underway and a feasibility study has just been finished [17].

### *Draught of cold air*

Patients with breathlessness often report that a draught of fresh air through an open window or a fan is helpful in reducing the feeling of dyspnoea. Schwartzstein showed that a flow of air to the face, nasal mucosa or pharynx may alter ventilation [18] but the exact mechanism behind this effect is unclear. It is postulated that cold receptors in the nose arising from the V2 distribution of the trigeminal nerve give sensory input to affect respiration and decrease breathlessness [10]. In healthy participants, a draught of cold air relieved induced breathlessness [18]. A hand-held fan is a simple and cheap device producing cold air. Two studies tested this simple intervention: a small pilot study did not show sufficient improvement but an adequately powered cross-over trial showed a significant improvement of breathlessness in patients with COPD and cancer [19].

### *Walking aids*

Promising results come from studies testing the effect of walking aids such as rollators on breathlessness

[20–25]. Three studies showed a significant improvement [20, 22, 24] and two a non-significant improvement of breathlessness as well as an increased walking distance [23, 25]. The positive effect of a walking aid on breathlessness is probably due to increased maximal voluntary ventilation by bracing the arms on the walking aid and adopting a lean forward position [23]. Stabilizing the ribcage may improve accessory muscle function allowing these muscles to be engaged in respiratory activities [23]. A further component could be the support of leg muscles. Although these studies have only been conducted in COPD patients, rollators are widely available and they may be worth a trial in cancer patients.

#### *Neuro-muscular electrical stimulation (NMES)*

Deconditioning and peripheral muscle weakness are known to play a major role in breathlessness in COPD [26]. Therefore exercise training is a key component of pulmonary rehabilitation programmes. However, not all participants with severe COPD are capable of exercise and exercise training [27]. To overcome this, NMES of leg muscles, mainly quadriceps muscle, seems to be an interesting alternative. Three studies tested the effect of transcutaneous NMES of leg muscles on breathlessness in COPD patients [27–29]. NMES was applied between 15 and 30 minutes, either five times per week for six weeks [29] or three days per week for six weeks [28] or 16 sessions over four weeks [27]. All three studies were able to show a significant decrease of breathlessness. The intervention was well tolerated by participants in all studies. To prevent development of more severe breathlessness, the best timing for NMES has to be defined but it can be assumed that earlier and regular treatment should be recommended. As muscle weakness is also known to be an associated factor in breathlessness in cancer patients [30] this intervention seems to be suitable to be tested in this group. A first study was successfully undertaken in patients with lung cancer but breathlessness was not included as an outcome [31].

## Pharmacological management of breathlessness

### *Opioids*

Opioids are the first line treatment in the pharmacological management of refractory breathlessness and the only treatment with evidence of a beneficial effect at the moment. The main evidence in this field comes from a systematic review with meta-analysis [32] and a

randomised control trial [33]. Jennings et al. included 18 randomised controlled trials (RCTs) studying patients with COPD (14 studies), cancer (two studies), chronic heart failure (one study) and interstitial lung disease (one study). The authors concluded that there is a strong evidence for a small and probably clinically significant effect of oral and parenteral opioids in the treatment of breathlessness [32]. The overall SMD (standardised mean difference) for oral and parenteral opioids was  $-0.40$  (95% CI  $-0.63$  to  $-0.17$ ;  $p = 0.0006$ ), which reflects an absolute clinical improvement of 8 mm on a 100 mm VAS. This seems to be small but could be a clinically significant relief for a patient with refractory breathlessness. There was no evidence to support the use of nebulised morphine, although the number of studies included in the meta-analysis was limited to three studies. However, a recent systematic review (including nine studies in COPD patients) confirmed the conclusion from Jennings et al. [34]. One limitation of the Jennings' review was the small number of participants in each study included. In 2003, Abernethy et al. published the first and still the only fully powered RCT to determine the efficacy of oral morphine in the relief of breathlessness in 38 opioid naïve patients (mainly patients with COPD) [33]. This study showed a statistically and clinically significant benefit of oral morphine in the relief of breathlessness with an improvement of 7–10 mm on a VAS.

Respiratory depression due to opioids is a major concern of many physicians, which is mainly based on the experience in anaesthesia where opioids are used for sedation. However, it is of great importance for daily practice that there is no evidence for respiratory depression when using opioids for the relief of breathlessness with an appropriate titration to reach the effective dose. Irrespective of the disease group, none of the studies mentioned above showed respiratory depression after the intervention [32, 33].

Adverse effects of opioids occur frequently in patients who receive opioids for the first time. Nausea, constipation and drowsiness are the most common adverse effects [35], but are well preventable and treatable.

There are still many unanswered questions regarding the treatment of breathlessness with opioids:

1. Which opioid is best for the treatment of breathlessness (e.g. morphine, hydromorphone or fentanyl)? Are there differences between different opioids?
2. Which dose is the appropriate starting dose for opioids naïve patients and for patients already using opioids?

3. Can we predict which breathless patient will respond to the treatment with opioids and who will benefit (e.g. genetic markers)?
4. Which mode of application is most effective for episodic breathlessness with a fast onset of action (e.g. sublingual or intranasal)?

More studies and fully powered RCTs are needed in the future to answer these questions and some studies are already underway.

## Benzodiazepines

Benzodiazepines (e.g. diazepam, midazolam, and lorazepam) are a group of drugs with a sedative-hypnotic, anxiolytic and muscle-relaxant effect, which interact with subunits of the central GABA receptors. The main therapeutic uses are insomnia, anxiety disorders and acute epilepsy. Benzodiazepines are frequently used in the management of breathlessness in advanced diseases and regularly recommended in clinical guidelines in palliative medicine [36]. However, a recent systematic review and meta-analysis found no evidence for a beneficial effect of benzodiazepines in the relief of breathlessness in advanced disease [37]. There is a slight but non-significant trend towards a beneficial effect but the effect size is small. This review identified seven controlled studies out of 1309 articles (last update September 2009), including two unpublished studies. studies were RCTs. The included trials studied a total of 200 patients with advanced stages of COPD and cancer. Different benzodiazepines were tested in different doses, including midazolam, alprazolam, diazepam and clorazepate. A meta-analysis including six out of seven studies with 235 observations of 171 patients showed no beneficial effect at a significant level with a small effect size of  $-0.32$  (95% CI  $-0.89$  to  $-0.24$ ). Sensitivity analysis demonstrated no differences regarding type of benzodiazepine, dose, mode and frequency of administration and duration of treatment. However, number of studies and included participants were small, so the result must be treated with caution.

Drowsiness and somnolence were the main reported adverse effects, which are well known as common effects of benzodiazepines. However, the clinical relevance of these adverse effects was mostly reported as mild or moderate and there was no difference between the intervention and control group with regard to attrition. It is important to state that respiratory depression was not observed in any of the studies.

Five out of seven studies measured anxiety as secondary outcome but no study could find an effect of benzodiazepines compared to placebo on anxiety. There is a strong relation between breathlessness and panic anxiety but there are still a lot of unanswered questions regarding pathophysiology, diagnosis and the optimal management regime of both [8, 39, 40].

In summary, there is no evidence for a beneficial effect of benzodiazepines in the relief of breathlessness at the moment. If other treatment options such as morphine and non-pharmacological measures fail benzodiazepines might be an option as second or third line treatment within an individual therapeutic trial. Benzodiazepines are safe without evidence for respiratory depression and the adverse effects are mainly clinically tolerable.

## Other anxiolytics and antidepressants

Anxiety and depression are highly prevalent in patients with breathlessness and need adequate treatment with anxiolytics and antidepressants. In addition, clinical experience suggests that anxiolytics such as buspirone and antidepressants such as mirtazapine and sertraline might have a specific role in the relief of breathlessness. However, two RCTs studying buspirone in 16 and 11 COPD patients showed contradictory results [41, 42]. Another RCT comparing buspirone with placebo is still recruiting and this study will hopefully bring further information about the efficacy of buspirone in the relief of breathlessness [43]. One RCT found no improvement of breathlessness in 30 patients with COPD and depression after treatment with nortriptyline [44]. Another study reported a reduction of breathlessness in seven patients with COPD after the application of sertraline but this was only a case series without a control group [45]. At the moment, there is not enough evidence to support the use of anxiolytics and antidepressants in COPD or cancer patients for the relief of breathlessness and further research is needed to make clear recommendations.

### *Phenothiazines*

Phenothiazines such as chlorpromazine, promethazine and levomepromazine are mainly used as anti-psychotic (e.g. chlorpromazine) or sedative and antihistaminic (e.g. promethazine) drugs with a large variety of effects (e.g. antiemetic, anticholinergic, anti-dopaminergic, and antiadrenergic). There are some clinical experiences from respiratory and palliative medicine using these drugs for the relief of

breathlessness and they are mentioned in some guidelines [46]. However, the scientific evidence is sparse. Seven studies examined promethazine or chlorpromazine in healthy participants [47–49], patients with COPD [50–52] and only one observational trial in terminal cancer patients [53]. All studies are small (6–20 participants) but most of them are RCTs. Three studies showed a significant improvement of breathlessness [47, 51, 53] and three studies could not find any improvement [49, 50, 52]. One study reported

even a deterioration of breathlessness after the application of promethazine [48]. Therefore, phenothiazines can currently not be recommended on an evidence base but they may be justified as a second or third line treatment within an individual therapeutic trial (n of 1).

*Inhaled furosemide*

Furosemide is a diuretic drug to increase water elimination of the body and is used mainly for heart failure,

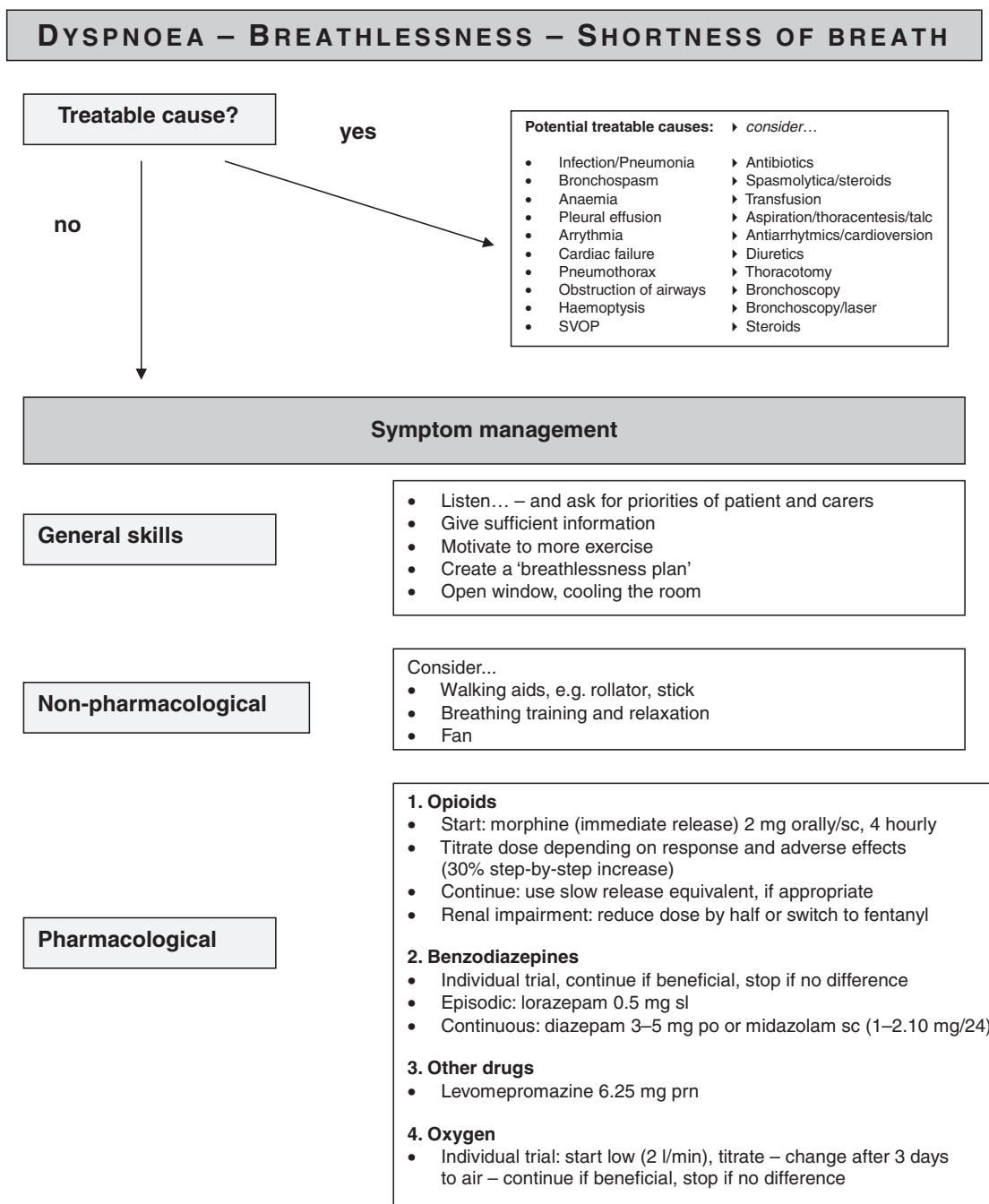


Fig. 1: Management of breathlessness

oedema and ascites. A recent review assessed the available evidence of furosemide in the relief of breathlessness and included eleven papers assessing breathlessness in patients with terminal cancer, COPD and healthy participants [8]. All studies examined only a small number of participants (1–35). Responses varied widely. The mean data showed only a small effect, which obscured the fact that furosemide proved to be very effective in some participants. A fully powered cross-over RCT in 15 cancer published after the review did not support a beneficial effect of nebulised furosemide [54]. The mechanism of furosemide in the relief of breathlessness beyond the effect of diuresis is still unclear, yet it is the object of current research. Furosemide seems to have a protective effect against bronchoconstriction [55]. Other hypotheses are related to the mechanism of J-receptors, which are involved in pulmonary oedema and to lung-stretch receptors that influence the central perception of lung expansion [8].

### Oxygen

Oxygen is widely used for the palliation of refractory breathlessness in advanced disease. However, a recent systematic review found no evidence for a consistent beneficial effect of oxygen in the relief of breathlessness in advanced disease [56]. Eight studies which compared the use of oxygen and air included a total of 144 participants with chronic heart failure, cancer and kyphoscoliosis (excluded COPD patients). Some cancer patients reported a benefit using oxygen but predictors and selection criteria (e.g. hypoxemia) could not be identified [56, 57]. Oxygen saturation has a weak correlation to the sensation of breathlessness and is not a valuable predictor for a beneficial effect of oxygen [58]. Adverse effects and burden of oxygen must be considered carefully taking into account e.g. the restriction of activity and communication. An RCT conducted by Abernethy et al. determined the effectiveness of oxygen in the palliative setting and has just finished the recruitment. Preliminary data analysis supports the decision about the prescription of oxygen on a case-by-case basis [59]. They concluded that patients are able to assess the net benefit and only a minority seems to benefit from oxygen therapy and that patients are unlikely to continue the treatment. Therefore, an individual trial (n of 1) is recommended to assess the effect of oxygen and air. When air has the same (or even better) effect than oxygen the recommendation of a fan should be considered. Oxygen should be prescribed only if it shows a clear benefit

for the patient. At the end of life, oxygen is rarely helpful and is often a misleading activity and distracting intervention for the patient and the carer. Morphine or benzodiazepines (if sedation is needed) are here the better treatment options.

## Conclusion

Management of refractory breathlessness in patients with advanced cancer is still challenging but there is some evidence for non-pharmacological and pharmacological treatment options. Both approaches are best combined and a management summary is shown in Fig. 1.

Most evidence for non-pharmacological interventions is coming from studies in COPD patients but walking aids and neuro-muscular electrical stimulation are also worth considering in cancer patients. A (hand-held) fan seems promising and is easy and cheap. More evidence is coming from various forms of breathlessness services although they are more expensive and need to be set up formally. Oral or parenteral opioids are the first line treatment in the pharmacological management. There is currently no evidence for a consistent beneficial effect for benzodiazepines, phenothiazines, antidepressants, inhaled furosemide and oxygen. Further studies are needed to clarify some unanswered questions in this area, such as dosing of opioids, effectiveness of inhaled furosemide, phenothiazines and antidepressants and the use of benzodiazepines in combination with opioids.

## Conflict of interest

The authors declare that there is no conflict of interest.

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