Palliative Care Concepts in Respiratory Disease

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Key Words

Chronic obstructive pulmonary disease • Dyspnea • Palliative care • Respiratory disease

Abstract

Many respiratory diseases besides lung cancer are still not curable. There is an unmet need for palliative care, especially in non-malignant conditions. In this article we focus on symptomatic treatment of typical symptoms in respiratory disease beyond causal treatment.

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Introduction

Albeit the many advantages in the field of respiratory medicine, many diseases still have a grim prognosis. This is not only true for lung cancer but also for severe chronic obstructive pulmonary disease (COPD), interstitial lung diseases, pulmonary hypertension and neuromuscular disorders leading to respiratory failure. Besides curative treatment, there is an unmet need of symptomatic treatment in advanced disease especially for non-malignant conditions. For example, patients with advanced COPD have a similar symptom burden compared to patients with lung cancer [1] and comparable prognosis [2, 3]. However, they have less access to palliative care [4].

In this article, we want to highlight symptomatic treatment options for patients with pulmonary diseases beyond disease-specific therapy.

Dyspnea

Dyspnea is a common symptom of lung diseases, and patients use variant terms to describe this condition, also conferred to as ‘the language of dyspnea’: ‘chest tightness’ is often experienced in coronary disease as well as in bronchoconstriction. ‘Rapid shallow breathing’ might be a sign of a mismatch between respiratory drive and lung compliance, as in interstitial lung disease. ‘Air hunger’ might be a sign of increasing carbon dioxide retention as long as ventilatory drive is still a function of the carbon dioxide level in the blood. Some patients complain of not to getting rid of the air, a sign of hyperinflation [5].

Previous articles in this series: 1. Boehler A, Herth FJF: Palliation in lung diseases – facing the challenge and new hope: introduction. *Respiration* 2011;82:109–110. 2. Gompelmann D, Eberhardt R, Herth FJF: Advanced malignant lung disease: what the specialist can offer. *Respiration* 2011;82:111–123. 3. Kreuter M, Herth FJF: Supportive and palliative care of advanced nonmalignant lung disease. *Respiration* 2011;82:307–316. 4. Maio G: Can help for patients be too expansive? Ethical considerations and end-stage lung disease. *Respiration* 2011;82:395–399.

Non-Pharmacological Approaches to Dyspnea

Handheld Fans

The use of handheld fans to produce increased flow to the airways has been investigated by Galbraith and colleagues [6]: 50 patients with dyspnea were randomized to hold a handheld fan towards their nose or to their leg first and then crossed over. The primary endpoint was a reduction of 1 cm on a 10-cm visual analog scale for dyspnea. There was a significant reduction in the sense of dyspnea in patients holding the device towards their face ($p = 0.003$). A Cochrane review did not detect a significant benefit for this intervention [7]; however, it was published before the above mentioned work. Because of its low cost it is justified to try this device in a patient with refractory dyspnea.

Noninvasive Mechanical Ventilation

Noninvasive mechanical ventilation is frequently used in patients experiencing acute or chronic respiratory failure. An advantage over invasive mechanical ventilation is the fact that patients do not need deep sedation and that interruption of treatment is possible. These features help patients to keep their self-determination. Intermittent noninvasive mechanical ventilation in COPD may not prolong life but can improve quality of life measured with different tools [8]. The indications for noninvasive ventilation in chronic respiratory failure due to COPD are outlined in table 1 [9]. There is no reported benefit in patients with restrictive lung diseases and it is questionable whether such measures should be instituted in the terminal phase of an illness. Trials comparing medical treatments with noninvasive ventilation in this situation are lacking.

Walking Aids

The use of a walking aid like a rollator allows the patient to rest with his arms on the device and thereby activate accessory breathing muscles. Also, the forward-leaning position might alleviate dyspnea [10]. However, evidence for this approach is weak at best [7].

Pulmonary Rehabilitation

In patients with COPD, the most effective single measure to alleviate dyspnea is pulmonary rehabilitation [11]. Although it does not directly improve gas exchange or lung mechanics, it improves muscle function allowing higher exercise tolerance and thereby reduces lactic acidosis.

Table 1. Indications for intermittent non-invasive ventilation (see text)

Symptoms of ventilatory failure like dyspnoea, fatigue, morning headache
and
Hypercapnia >55 mm Hg in arterial blood
or
Hypercapnia 50–54 mm Hg and nocturnal desaturations despite supplemental oxygen (2 liters/min)
or
Hypercapnia 50–54 mm Hg and at least two hospitalizations per year due to hypercapnic exacerbation

Another benefit of exercise training is the diminished ventilatory demand resulting in a lower respiratory rate. Thereby expiration is prolonged and dynamic hyperinflation reduced [12].

Pharmacological Approaches to Dyspnea

Oxygen

Patients with dyspnea often request supplemental oxygen. However, benefit in terms of prolonged survival depends on a number of factors which were identified more than 30 years ago in a trial by the Nocturnal Oxygen Therapy Trial Group: 203 patients with COPD and hypoxemia were randomized in one group receiving nocturnal oxygen for approximately 12 h/day and in another group receiving continuous oxygen. The risk of death was 1.94-fold higher in the nocturnal oxygen group compared to the continuous oxygen group with a 2-year mortality of 40.8% in the former group compared to 22.4% in the latter, as long as oxygen use exceeds 16 h/day. This effect was seen irrespective of the presence or absence of hypercapnia [13]. In another trial, 87 patients with COPD, hypoxemia and carbon dioxide retention were randomized to either oxygen supplementation at a rate of 2 l/min for at least 15 h/day or no oxygen supplementation. Five-year mortality was reduced in the oxygen group (45.2%) compared to the control group (66.7%) [14].

Evidence of supplemental oxygen in interstitial lung diseases is sparse if present at all: in a trial by Strom and Boman [15], 240 patients with parenchymal lung disease and supplemental oxygen therapy were followed for 28 months. There was no control group, and many patients had restrictive lung disease due to sequelae of tuberculosis with deformities of the chest wall. Also, COPD was present as a comorbidity in many patients. Low $p\text{CO}_2$

Table 2. Key studies regarding long-term oxygen therapy

Study	NOTT	MRC	Górecka et al. [17]	Fletcher et al. [18]	Chaouat et al. [19]
n	203	87	135	38	76
Mean pO ₂ (mm Hg) pre	44	54	59	<60, nocturnal desaturation	56–69, nocturnal desaturation
Duration of observation	19 months	60 months	36 months	36 months	35 months
Hours on oxygen per day	16	15	15	nocturnal	nocturnal.
Parameter	Mortality	Mortality	Mortality	Mortality/PAP	Mortality/PAP
Results	+ (40.8 vs. 22.4%)	+ (66.7 vs. 45.2%)	negative	negative	negative

(<5.5 kPa), poor performance status and the presence of interstitial fibrosis were predictors of poor outcome. Although there is no evidence for prolonged survival in this patient group, exercise tolerance is improved with supplemental oxygen at higher flow rates [16].

The German guideline for long-term oxygen therapy states that patients must have hypoxemia (≤ 55 mm Hg partial pressure of oxygen in arterial blood gas) or right heart failure with an arterial blood gas <60 mm Hg [16] (table 2). These conditions are seldom fulfilled. The question is whether supplemental oxygen at least relieves dyspnea in patients not matching the above mentioned criteria. In a randomized trial, patients with refractory dyspnea, incurable disease and a partial pressure of oxygen >7.3 kPa (approximately 55 mm Hg) were randomly assigned to oxygen or room air delivered by a nasal cannula with a flow of 2 l/min, at least 15 h daily for 7 days. The dyspnea on day 6 changed by –0.9 points (on a 1- to 10-point scale, with 10 denoting maximum dyspnea) in the oxygen group compared to –0.7 in the room air group representing a nonsignificant difference ($p = 0.554$). Drowsiness was more frequently reported in the room air group (13 vs. 10%), as well as nasal irritation (6 versus 2%). These findings do not justify the use of oxygen in this patient group [20].

Opioides

The only drugs with a proven effect on dyspnea are opioids. Opioid receptors are found in high densities in the brain stem and may exert an inhibitory influence on respiratory drive mainly mediated by μ -receptors. Moreover, opioids have anxiolytic properties further diminishing dyspnea. Opioid receptors in the lung itself are also postulated, because nebulized inhaled morphine seems to have a moderate effect on dyspnea [21, 22]. However, only systemically administered morphine has a significant measurable effect on dyspnea at rest (–0.9 on a scale of 1–10, with 10 denoting maximum dyspnea) [23] and the precise mechanism of action is not known yet. Routes

of administration depend on the severity of the symptom. In acute dyspnea, opioids should be given intravenously or subcutaneously; intranasal or buccal fentanyl is a reasonable alternative. Chronic dyspnea can be alleviated by slow-release formulations given on a regular schedule.

Benzodiazepines

Benzodiazepines do not have a significant effect on dyspnea itself but they diminish anxiety as a trigger of acute dyspnea, thereby breaking the vicious circle of anxiety and dyspnea.

In a trial of alprazolam in chronic dyspnea there was no benefit observed: 29 patients were randomized to 0.5 mg of alprazolam twice daily or placebo. There was no difference in chronic dyspnea as measured with the Medical Research Council score and no improvement in distance in the 12-min walking test [24]. In this trial, although drowsiness occurred, benzodiazepines were well tolerated.

Neuroleptic Drugs and Antidepressants

Neuroleptic drugs like chlorpromazine were studied in COPD patients, but the results were conflicting [25]. The same accounts for antidepressant drugs, so their use cannot be recommended for the relief of dyspnea [10].

Cough

Cough is initiated by rapidly adapting ‘irritant’ receptors located in the larynx and major airways, especially at the branching points of the tracheobronchial tree. They can be stimulated by a variety of factors like smoke, histamine or foreign bodies. Its physiological task is clearance of the airways from foreign bodies or mucus. In healthy subjects, cough accounts for approximately 2.5% of mucociliary clearance while in patients with chronic bronchitis it accounts for 20% [26]. It is important to assess whether the cough is productive or not and if there is any identifiable trigger or time in which cough occurs.

Also, a thorough review of a patient's medication is of paramount importance. By doing this, causal treatment of this symptom is sometimes possible, i.e. by identifying asthma or a particular medication (i.e. angiotensin-converting enzyme inhibitors) as the cause. Unfortunately, the majority of patients with advanced pulmonary disease need symptomatic treatment as outlined below.

Non-Pharmacological Approaches to Cough

Cough is a physiological mechanism to clear the airways. Making cough more effective is therefore a reasonable approach for alleviating this symptom. Evidence regarding non-pharmacological approaches to cough stems from trials conducted 20–30 years ago. One method is manual compression of the chest by a second person during the expiratory phase of coughing and thereby enhancing the peak expiratory flow. But besides the drawback of needing a second person for this maneuver, it is not applicable for patients with a stiff chest or after abdominal surgery. Other physiotherapeutic opportunities are postural drainage and thoracic vibration. With postural drainage, gravity is used to improve mucociliary clearance by positioning the patient head down. However, there is only sparse evidence for patients with cystic fibrosis indicating that postural drainage may help. For other diseases, the benefit is uncertain. Thoracic vibration is sometimes used in addition to postural drainage. Again, there are sparse and conflicting data regarding the efficacy of this approach. The frequencies of the used devices in the studies differ, making comparison even more difficult [27, 28]. A pipe-like device called 'Flutter' uses the same principle: in the pipe, a steel ball oscillates by breathing into the mouthpiece and thereby generates vibrations in the airways. The oscillation can be modulated by changing the inclination of the pipe. Again, evidence of efficacy is sparse [29].

Application of positive expiratory pressure (PEP) via a face mask during cough showed disappointing results in patients with cough due to chronic bronchitis. Forty-seven patients with COPD and hypersecretion were randomized to at least 45-min daily treatment with PEP with either 10 or 0 mm Hg (placebo). After 6 months of treatment, the amount of sputum and dyspnea was similar in both groups. Dyspnea on exertion and cough significantly improved in the placebo group. Therefore, the authors did not recommend the use of PEP masks [30]. However, in another report from the same year, 43 patients with COPD were allocated to standard physiotherapy or PEP used twice daily. PEP resulted in improvement of cough

and less mucus production [31]. In a meta-analysis regarding patients with cystic fibrosis [32], the authors concluded that PEP was equally effective as standard physiotherapy.

Pharmacological Approaches to Cough

Existing evidence is on a low level or even only expert opinion. Medications to treat cough can be divided into two categories: those making cough more effective and those inhibiting the cough reflex.

The so-called 'mucolytics' N-acetylcysteine and ambroxol are frequently prescribed in acute cough. However, well-controlled clinical trials documenting a benefit in chronic cough do not exist and even the mechanism of action is not known [33].

Centrally acting inhibitors of the cough reflex include non-opioid drugs like dextromethorphan and opioid drugs, mainly codeine and its derivatives as well as morphine. In a small crossover trial with 16 patients suffering from chronic cough, either 20 mg of codeine or dextromethorphan was given daily. Cough frequency was lowered equally in both groups; however, the intensity was significantly lowered in a greater degree with dextromethorphan ($p < 0.0008$). Patients thus considered dextromethorphan to be the better antitussive ($p < 0.001$) [34]. However, because of the low number of patients, these results have to be viewed with caution. Another observational trial included no more than 8 patients comparing 30 mg of codeine to 60 mg of dextromethorphan and found both regimens equally effective [35]. Again, the number of patients precludes significant conclusions.

Slow-release morphine was investigated in a double-blind, crossover trial including 27 patients. Inclusion criteria were cough of >3-month duration and failure of specific therapy. Patients were randomized to either 5 mg of slow-release morphine twice daily or placebo. A reduction of 40% in daily cough scores was achieved with daily morphine ($p < 0.01$ compared to placebo) [36]. There is no evidence for a dose-dependent effect of opiates nor is there any superiority proven for any specific opioid over another [37].

Giving systemic steroids (30 mg daily for 2 weeks) is always worth a try, especially in patients with cancer [37]. Inhaled steroids seem to be effective only in the presence of airway inflammation and had no effect on non-asthmatic cough [38].

Inhaled ipratropium bromide blocks the efferent limb of the cough reflex and alters mucociliary factors and

Table 3. Drugs against cough

Drug	Proposed dosage
Dextromethorphan	10–15 mg two to four times daily
Codeine	30–60 mg four times daily
Morphine	5–10 mg of slow-release formula twice daily
Prednisolone	30 mg daily for two weeks
Nebulised lidocaine	5 ml of 0.2% solution twice daily
Inhaled ipratropium bromide	500 µg in 2 ml solution four times daily

Adapted from Molassiotis et al. [37].

Table 4. Possible contributing factors to fatigue

Factor	Example
Side effects of medication	chemotherapy, opiates, metoclopramide
Endocrine aberrations	hypothyroidism, hypogonadism
Comorbidities	depression
Metabolic alterations	hypercalcemia, hypoxemia, dehydration
Cytokines	interleukin 1, interleukin 6 ¹
Infection	pneumonia

¹ [41].

thereby decreases stimulation of cough receptors. However, the only evidence comes from a group of 14 patients with chronic persistent cough following an upper respiratory tract infection: in a crossover design, 320 µg of inhaled ipratropium daily significantly reduced day- and nighttime symptoms. Notably, bronchial hyperreagibility was ruled out by methacholine testing [39].

Inhaled local anesthetics are recommended for cancer-related cough in a review by Molassiotis and colleagues [37]. This approach has to be used with caution because of the possibility of reflex bronchospasm. The patient should avoid oral intake for at least 1 h after inhalation because of the anesthetized pharynx and the possibility of aspiration.

Table 3 summarizes the available drugs for symptomatic treatment of cough.

Fatigue

Fatigue is a main symptom of malignant conditions, especially in lung cancer. But also in nonmalignant pulmonary diseases, fatigue is a major issue. Fatigue is defined as tiredness in a physical, emotional or cognitive dimension which is out of proportion to the recent activity and interferes with the activities of daily living [40]. It is a condition caused by multiple factors (table 4); many of them are poorly understood. To identify a treatable cause is the first step encountering this problem. One should consider hypoxemia, dehydration, electrolyte imbalances – especially hypercalcemia in malignant conditions –, hypothyroidism and anemia as possible triggers. It is mandatory to inquire for depression as well. In many cases, no treatable cause will be identified or treatment of the assumed cause does not relieve the symptom.

Non-Pharmacological Approaches to Fatigue

There are several approaches to treat fatigue with different underlying pathophysiological assumptions, summarized in the PACE Study by White and colleagues [42] regarding the chronic fatigue syndrome: if one considers fatigue to be a true lack of energy, adaptive pacing (APT) is a reasonable strategy. It is a behavioral therapy guiding the patient to plan and pace activities and thereby reducing or avoiding fatigue. Cognitive behavior therapy (CBT) is based on the assumption of a vicious circle of fear of fatigue and avoidance of activity perpetuating fatigue. Patients are advised to gradually increase mental and physical activities after they have learned about their baseline energy level in experimental tasks. If one considers fatigue to be a result of physical deconditioning due to the underlying illness, graduate exercise therapy (GET) makes sense. Patients increment their daily exercise (i.e. walking) in predefined steps avoiding overexertion.

These three approaches haven been compared to each other as well as to specialist medical care (SMC) which consists of explaining the nature of fatigue to the patient and counseling, for example to avoid extreme periods of rest or exercise. Six hundred and forty-one eligible patients were randomized to APT (160 patients), CBT (161 patients), GET (160 patients) and SMC alone (160 patients). Fatigue was significantly reduced with CBT (3.4 points on the Chalder fatigue questionnaire from 0 to 33 where the lowest score is least fatigue; 95% CI 1.8–5.0; $p = 0.0001$) and GET (3.2 points; 95% CI 1.7–4.8; $p = 0.0003$) compared to SMC alone. There was no difference between APT (0.7 points; 95% CI –0.9 to 2.3; $p = 0.38$) and SMC alone. Also, the mean physical function scores im-

proved significantly with CBT and GET compared to SMC alone but not with APC.

A major limitation of this study is the fact that chronic fatigue syndrome per definition precludes fatigue in organic disease and it is not known whether these results also apply to the latter patient group.

Another non-pharmacologic approach, especially in patients with COPD, is pulmonary rehabilitation. Besides many other beneficial effects, pulmonary rehabilitation can alleviate fatigue: in a recently published study, a cohort of 81 male patients with COPD was followed regarding a change in the disease-specific quality of life. The dyspnea, mastery, emotion and fatigue domains of the Chronic Respiratory Questionnaire Self-Reported were measured from baseline to completion of pulmonary rehabilitation. A significant reduction in fatigue after pulmonary rehabilitation was observed ($p = 0.017$) [43].

Pharmacological Approaches to Fatigue

Drug treatment of fatigue is almost exclusively investigated in cancer patients. To the knowledge of the authors, no relevant trials of fatigue treatment in nonmalignant disease exist.

In the case of fatigue accompanied by a low hemoglobin level (<10 g/dl), a blood transfusion can sometimes ameliorate this clinical symptom. In a feasibility study, 30 patients with cancer-related fatigue and anemia answered two different fatigue scales (the Functional Assessment of Cancer Therapy Fatigue and the Brief Fatigue Inventory) before and 3 days after a blood transfusion. There was a significant improvement in both scales measured after transfusion [44].

Administration of colony-stimulating factors is investigated in cancer patients, as guidelines regarding this issue exist. However, the use of erythropoietin and its analogues has major drawbacks: the onset of action is delayed for several weeks after injection, there is concern of increased tumor growth in cancer-related anemia and the costs are high. These drugs are thus only recommended in chemotherapy-related anemia [45].

Methylphenidate is a phenethylamine with indirect sympathicomimetic properties. This centrally acting drug possesses structural similarities to amphetamine and as a psychostimulant is used in attention-deficit hyperactivity disorder but also – off label – in cancer-related fatigue. A large phase III trial compared the administration of methylphenidate to placebo: 74 patients in each arm received either 54 mg of extended release methylphenidate or placebo for 4 weeks. The primary endpoint was a subjective change in the patient's fatigue measured by

the Brief Fatigue Inventory. In the whole cohort, there was no difference after 4 weeks in the two groups ($p = 0.317$). However, in the patients with worst fatigue, there was a trend for an improved outcome in the methylphenidate group. Typical side effects of methylphenidate are nervousness and loss of appetite [46].

In a meta-analysis on pharmacological treatment of cancer-related fatigue – published before the above mentioned study – methylphenidate had a small but significant beneficial effect on fatigue [47]. However, these results do not apply to nonmalignant respiratory diseases where no nonspecific treatments of fatigue have been investigated.

Cachexia

Cachexia occurs in cancer patients as well as in patients with nonmalignant lung diseases, i.e. COPD.

In COPD, the term 'pulmonary cachexia' is frequently used but only vaguely defined as a loss of lean body mass regardless of calorie intake. Although the mean body mass index (BMI) in COPD patients is overall not different from healthy subjects with values between 25 and 26 [48, 49] the distribution is different, with a larger portion of underweight subjects. In a cohort of patients with moderate to severe COPD, the prevalence of nutritional depletion [defined as $\text{BMI} \leq 21$ and/or fat-free mass index ≤ 15 (in females) or ≤ 16 (in males)] was high (27%) [50].

The causes of pulmonary cachexia are not completely understood. Postulated mechanisms include elevated total caloric expenditure due to higher respiratory effort, inefficient metabolism of substrates and increased levels of proinflammatory cytokines [51]. A low BMI is an independent risk factor for a poor prognosis in COPD [52]. This is possibly due to a loss of muscle mass and associated low exercise tolerance.

Cachexia in cancer has not been defined precisely, thus making comparisons of results of clinical trial populations difficult. This problem has recently been addressed by an international consensus conference. A key issue in this process was the description of a continuum with three defined stages rather than a single state. Pre-cachexia is defined as an anorectic state with weight loss of $\leq 5\%$ of body weight. This can transit into cachexia, defined as weight loss of >5 or $>2\%$ in patients with a preexisting low BMI of ≤ 20 or sarcopenia. The latest stage in this definition is refractory cachexia which is defined by a therapy-resistant, procatabolic underlying illness with poor performance status and a survival prognosis of <3 months [53].

Non-Pharmacologic Approaches to Cachexia

Noninvasive Ventilation

The implementation of noninvasive positive pressure ventilation (NPPV) might reverse pulmonary cachexia. In a cohort study, 141 patients with severe chronic respiratory failure due to COPD changes in BMI were evaluated between baseline, 6 and 12 months after initiation of NPPV. Overall, 20.6% of patients had a BMI <20 at baseline. These were the patients with the most severe respiratory impairment: there was a very high negative correlation between BMI and hyperinflation ($r = -0.55$, $p < 0.001$). In the patient group with a BMI <20, NPPV resulted in a significant weight gain of 6.2% ($p < 0.05$) at 6 months and 12.8% ($p < 0.01$) at 12 months, respectively. No weight gain was observed in subjects who had a BMI ≥ 20 [54]. In the whole study population, no correlation between BMI change and changes in other values of lung function like inspiratory muscle strength or blood gas values was observed. However, a major drawback of the study was the lack of a control group not receiving NPPV.

Counseling of Patients and Relatives

In cancer patients, relatives are more concerned about the patient's weight loss than the patients themselves. Especially in refractory cachexia, it is of paramount importance to help the family cope with this problem. Facing the poor prognosis, it should be avoided to force the patient to eat although there is no feeling of hunger. It should be explained that in this phase of the disease, the demand of nutrition is of very low importance because it will not alter the course of the disease. Relatives and friends should accept this instead of trying to make the patient eat.

Pharmacological Approaches to Cachexia

Cachexia as a complex syndrome can be addressed in several ways. First, one can try to increase appetite with ghrelin and its analogues, megestrol acetate or tetrahydrocannabinol (THC). Second, considering cachexia as an inflammatory state, targeting the acute-phase reaction with nonsteroidal anti-inflammatory drugs or steroids is reasonable. Third, the use of other drugs (whose mechanism of action on cachexia is not understood), i.e. the antidepressant mirtazapine, was investigated. To date, no drug is approved for treatment of cachexia due to respiratory diseases or cancer in the European Union.

Ghrelin and Anamorelin

The activation of ghrelin receptors stimulates appetite and increases lean body mass. However, because of its short half-life, ghrelin has to be administered by the parenteral route. This is not feasible in clinical practice. Anamorelin is an orally available non-peptidic drug, which mimics the N-terminal, active region of ghrelin. In 32 healthy volunteers, anamorelin resulted in dose-dependent weight gain [55]. Further studies with this drug in cancer patients are planned.

Megestrol Acetate

Megestrol acetate is a derivative of progesterone. In cancer patients, the administration of megestrol acetate results in increased appetite and weight gain. However, there was no improvement in survival or quality of life [56]. Thus, relying on the available data, megestrol acetate cannot be recommended for the treatment of cancer cachexia.

Tetrahydrocannabinol

The plant *Cannabis sativa* contains about 60 cannabinoids including THC and cannabidiol. Whereas THC has antiemetic and psychoactive effects, cannabidiol attenuates the psychotropic effects of THC and has anti-inflammatory properties. These drugs reportedly increase appetite. In a three-arm study, the effect of THC was compared to cannabis extract and placebo. The primary endpoint was a gain of appetite and quality of life with THC and cannabis extract compared to placebo. However, all groups reported similar proportions of patients with increased appetite (THC 58%, cannabis extract 73% and placebo 69%) resulting in an early termination of the study due to futility [57]. This makes cannabinoids a very questionable option for the treatment of cancer-related cachexia.

Mirtazapine

The antidepressant drug mirtazapine was associated with an increase in appetite. However, only a small study with 17 non-depressive patients with cancer-related fatigue exists. Twenty-four percent of these patients experienced weight gain with a dose of 15–30 mg daily [58]. These results do not justify the use of mirtazapine on a broad basis in cancer-related cachexia. Further studies are clearly needed.

Steroids and Nonsteroidal Anti-Inflammatory Drugs

Steroids have long been used for a variety of complaints in terminally ill patients. Dyspnea and fatigue as

well as cachexia are potential conditions treated with these drugs. Considering cachexia as an inflammatory condition, the use of steroids or other anti-inflammatory drugs makes sense. In a quite old paper by Lundholm and colleagues [58], 135 patients with malnutrition and various types of cancer were randomized into three groups: 10 mg of methylprednisolone, 50 mg of indomethacin or placebo daily. The primary endpoint was overall survival. Anti-inflammatory treatment indeed improved overall survival compared to placebo ($p = 0.03$); however, measures of weight gain or appetite were not reported [59]. In daily practice, we indeed observe an improvement in appetite in patients receiving methylprednisolone; however, that does not apply to all patients and it is not possible to predict who might benefit.

Conclusion

Evidence for palliative treatments in respiratory diseases is sparse, and relevant studies only exist for COPD. The other strategies are adopted from cancer patients, where far more trials have been done. In how far results can be generalized is questionable. Many drug treatments in palliative care are off label and need to be weighed against potential risks.

There is an unmet need of larger trials of palliative care interventions, especially in nonmalignant respiratory diseases.

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