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Interventions for alleviating cancer-related dyspnea: A systematic review and meta-analysis

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Abstract

Background. Dyspnea is commonly encountered by many cancer patients in the terminal stage of their disease and it severely hampers their quality of life. We aimed to evaluate the role of interventions to alleviate dyspnea. *Methods*. Systematic review and meta-analysis of randomized controlled trials assessing all interventions for dyspnea palliation in cancer patients, and searched the Cochrane Library, MEDLINE, conference proceedings, and references. *Results*. Our search yielded 18 trials. Eight studies evaluated opioids in any route of administration, seven studies evaluated the use of oxygen, two studies assessed the role of benzodiazepines and two studies evaluated the role of furosemide in alleviating cancer-related dyspnea. Weighted mean difference (WMD) was calculated for continuous variables that were reported on the same scale. For continuous data reported in different scales, standardized mean difference (SMD) was calculated. Meta-analysis of three trials yielded a positive effect for opioid administration, WMD −1.31[95% CI (−2.49)–(− 0.13)]. Meta-analysis of the six studies showed lack of benefit to oxygen to improve dyspnea, SMD −0.3[95% CI −1.06–0.47]. The role of benzodiazepines remains unclear, furosemide was not beneficial. *Conclusions*. Our systematic review and meta-analysis demonstrate a beneficial effect to opioids in alleviating cancer-related dyspnea, and no advantage for the use of oxygen.

Dyspnea is commonly encountered by more than 50% of patients with advanced cancer in the terminal stage of their disease, and often it is not well controlled [1–3]. In contrast to pain, the mechanism of cancer-related dyspnea is less understood. Dyspnea precipitates physical and psychological distress, severely hampers the patients' quality of life, and has been associated with both anxiety and depression [4–7].

The management of cancer-related dyspnea remains a challenge lacking systematic guidelines for clinical care. The arsenal of interventions includes opioids, oxygen, psychotropic drugs and nebulized furosemide.

Opioids have been used to treat dyspnea from various causes for more than a century, though due to the suggested correlation between opioids and respiratory depression their clinical use has been declined throughout the years. Most of the evidence regarding the role of opioids in alleviating dyspnea is derived from non-malignant conditions. In a meta-analysis of studies that evaluated opioids in treating breathlessness from various etiologies, a statistically significant positive effect on the sensation of breathlessness was found [8]. Nevertheless, opioids are not widely used for cancer-related dyspnea in terminally ill cancer patients and there are few randomized controlled trials (RCTs) that appraise opioids' role in this population.

The role of oxygen in the management of cancer-related dyspnea in non-hypoxic patients is questionable. There is a discrepancy between the widely clinical use of oxygen in cancer patients experiencing dyspnea and the lack of clinical benefit observed in RCTs and in a former meta-analysis [9].

In 2008 we had published a systematic review assessing the interventions for treating dyspnea in patients with advanced cancer, yet a meta-analysis was not feasible due to paucity of data [10]. Newer studies enabled us to perform an updated systematic review and meta-analysis of RCTs of interventions for alleviating cancer-related dyspnea. Due to a recent Cochrane review of non-pharmacological

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interventions for dyspnea, including cancer-related dyspnea [11], we focused on the various pharmacological interventions and the role of oxygen.

Methods

Study selection

We included RCTs assessing terminal cancer patients experiencing dyspnea in which any intervention for dyspnea relief was compared with no intervention, placebo, or another intervention, as previously described [10].

Data sources

We updated our literature search in PubMed (January 1966 to November 2011), CENTRAL (the Cochrane Library, up to 2011), EMBASE and conference proceedings in oncology. Our search term for PubMed was (opiate OR opioid OR morphine) OR benzodiazepine OR furosemide OR steroids OR corticosteroids OR oxygen OR pharmacological AND (cancer OR carcinoma OR malignancy OR neoplasm) AND(dyspnea OR breathlessness). This was incorporated with a highly sensitive search for RCT retrieval, previously described [10].

Data extraction and quality assessment

Two reviewers independently extracted data from included trials. In case of disagreement between the two reviewers, a third reviewer extracted the data and results were attained by consensus.

Comparisons

We defined the following comparisons a priori: 1) administration of any opioid, in any dose, by any route with the intention of alleviating breathlessness: opioids versus no treatment or placebo, opioids versus benzodiazepines, and opioids versus combination therapy (such as opioids plus benzodiazepines); 2) oxygen versus placebo (room air) or any other intervention (such as helium-enriched air); 3) furosemide versus placebo or no treatment; and 4) benzodiazepines versus placebo or no treatment.

Definition of outcomes and data synthesis

The primary outcomes were subjective dyspnea relief according to Visual Analog Scale (VAS) – preferably change from baseline to the end of follow-up or absolute VAS score at the end of follow-up, as defined in each study. Secondary outcomes included oxygen saturation and adverse effects. VAS typically have a 100 mm or 10 mm line with verbal descriptors such as "no breathlessness" and "worst possible breathlessness" at the ends. We standardized the data into a 10 mm scale to enable pooled analysis.

Since the design of most trials was a crossover design, we intended to perform a paired analysis in a meta-analysis (i.e. pooling the data of every cycle in each trial), nevertheless that was not feasible since only one study reported the data of every cycle separately. We therefore used the more conservative method of pooling all the data from the experimental arm and comparing it with all the data from the control arm at end of trial phase, and analyze these as if the trial was a parallel group trial of experimental arm versus control arm, in accordance with the Cochrane handbook [12].

Meta-analysis was performed for studies in which the means and standard deviation could be calculated from the reports. We calculated weighted mean difference (WMD) for continuous variables that were reported on the same scale (most commonly VAS scale). WMD represents the weighted combination of absolute differences between the mean values in the two groups in a clinical trial. This summary statistic has the same unit of measurement as the variable measured. For continuous data reported in different scales (different scales for assessment of dyspnea) we calculated standardized mean difference (SMD). In this summary statistic the differences between the mean values are standardized in each study for its standard deviation to achieve standard scale. Changes from baseline values rather than end values were analyzed preferentially. Where unavailable, we combined end values and change from baseline values. All results are reported with 95% confidence intervals (CI). All analyses were conducted using Review Manager, version 4.2 (The Cochrane Collaboration, Oxford, UK).

Since there was clinical heterogeneity between the trials, we chose to conduct the analysis using a random effects model (the DerSimonian and Laird method) [13] all statistical tests were two-sided.

Results

The literature search identified 829 publications. Of these, 97 were retrieved for further evaluation, and 78 were excluded for various reasons. Figure 1 describes the process of article retrieval and reasons for elimination.

Opioids

Eight RCTs assessed the effect of opioids in various routes of administration on cancer-related dyspnea (Table I) [6,14–20]. Five of them were crossover studies evaluating opioids versus placebo and

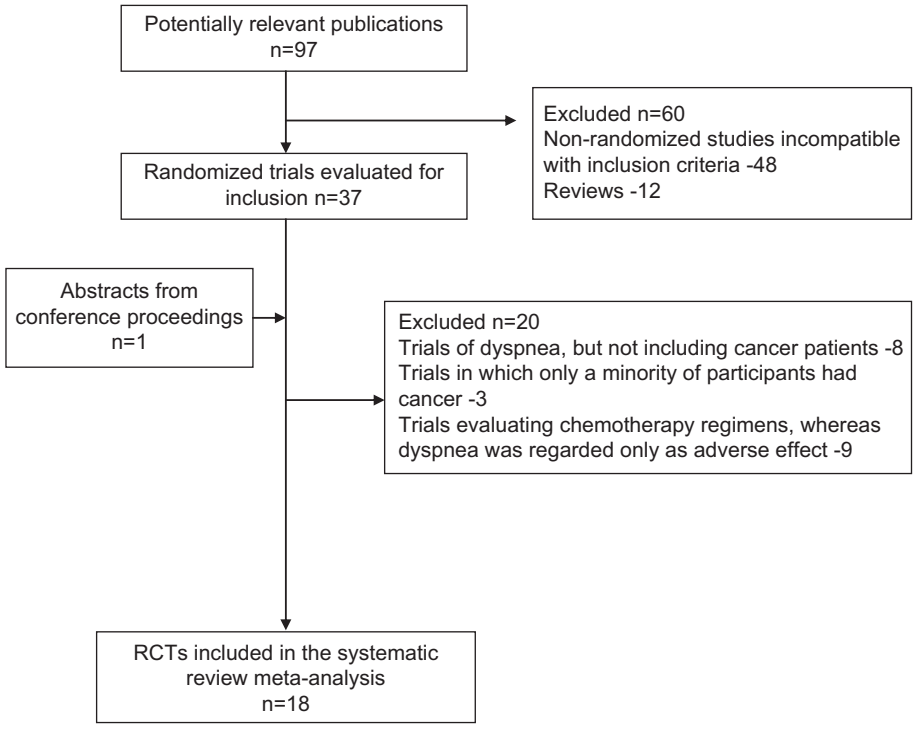

Figure 1. Randomized controlled trials search and selection.

included a total of 130 patients. Most trials included patients with lung cancer or lung metastases.

Meta-analysis was conducted only for trials that compared morphine to placebo. We excluded one trial that evaluated nebulized morphine versus placebo from the meta-analysis due to the reported dyspnea scale that differs in units from other studies and also due to the significantly better baseline values of the experimental (morphine) arm that subjected the trial to selection bias [19]. The study is included in the systematic review. Three studies shared a design that enabled the inclusion in a meta-analysis. They included a total number of 69 patients. All were double blinded, randomized controlled crossover trials. One study [16] evaluated two routes of opioid administration and hence every arm was pooled separately. Meta-analysis of three trials yielded a positive effect for opioid administration on dyspnea, WMD −1.31(95% CI −2.49, −0.13) (Figure 2). For the subcutaneous routeWMD was −1.58(95% CI −3.02, −0.18). Of note, in the study that compared nebulized morphine to subcutaneous morphine there was a trend in favor of the nebulized, and in another study, the nebulized route appeared more effective than the subcutaneous route [6,16], although meta-analysis for the nebulized mode only was not feasible. Two studies included only in the systematic review due to dissimilarity in methodology suggested the effect of nebulized morphine resulted in a trend only in higher dose or no benefit at all [18,19]. Systematic review reveals that opioids are beneficial in either opioid-naïve or -tolerant patients, in whom dose escalation depicts a better response [16,18].

Adverse events. Adverse events were reported in three of the seven morphine trials and two midazolam-morphine trials. No evident serious adverse effects such as respiratory depression and sedation were noted.

Oxygen

Six trials were included in the systematic review and meta-analysis with a total of 179 patients. In one study [21] the data was obtained for the subgroup of patients with cancer from the general study population. One study was only included in the systematic review due to its design, and presented in Table I. This study indicated a benefit for opioid and lack of benefit for oxygen [17]. The study characteristics are presented in Table II. The type of intervention was similar in five of the trials – oxygen (4 to 5 l/min) versus air and in one trial, oxygen was compared with helium-enriched air or medical air [26]. Two trials included only patients in the ambulatory setting, with saturation greater than 90% and hemoglobin level greater than 10 g/dl [21,23]. A recent trial by Abernathy et al. [21], had a longer duration of follow-up than other trials. Three trials also included hypoxic patients with saturation below 90% and

Table I. Included Trials, Opioid Use, Patient Characteristics and Study Design.

Study	Type of intervention	Patients (N)	Diagnosis (cancer type)	Patient characteristics Age (median), gender	Inclusion criteria	Exclusion criteria	Duration of intervention	Design of trial, methodology	Description of the intervention effect by study authors
Morphine vs. placebo (saline) any route									
Mazocatto, 1999	S/C Morphine vs. placebo (saline)	9	Lung 7p , breast 1p, bladder 1p	73 y (66–83) 4 women, 5 men	Age > 18, documented terminal advanced cancer, life expectancy less than a week, minimental > 23/30, severe dyspnea at rest, performance status 4	COPD with hypercapnia, CHF non-compensated, severe renal or hepatic failure, other uncontrolled symptoms that could require opioids	2 days	RCT, cross-over, double blind study, allocation generation: not reported, allocation concealment: not reported	Significant decrease in VAS measured 45 minutes after intervention Non-significant increase in nausea and somnolence
Bruera, 1993	S/C Morphine vs. placebo (saline)	10	Lung 7p, lung metastases 3p	Not reported	Patients with terminal cancer, fully conscious, normal cognitive status, complaining of shortness of breath, receiving continuous oxygen using nasal prongs	Not reported	5 days	RCT, cross-over, double blind study, allocation generation: not reported, allocation concealment: not reported	Significant decrease in VAS measured 45 minutes after intervention On completion of study more patients preferred morphine
Davis, 1996	Nebulized morphine 5–50 mg vs. placebo (nebulized saline)	79	Lung or lung metastases	60 y (20–81) 35 women, 34 men	Patients with breathlessness at rest due to known primary or secondary malignancy and radiological evidence of at least one of: pleural effusion, mass lesion, lymphadenopathy and lymphangitic carcinomatosis	Opioid intolerance or abnormal renal function	2 days	RCT, double blind study, allocation generation: not reported, allocation concealment: not reported	No significant improvement from baseline to 60-minute VAS A trend toward greater improvement in breathlessness with higher doses of morphine
Grimbert, 2004	Nebulized morphine sulphate vs. placebo (nebulized saline)	12	Lung or lung metastases	63 y 1 woman, 11 men	Not reported	Not reported	2 days	RCT, cross-over, double blind study,	Similar improvement from baseline in dyspnea scores with morphine or placebo reported by patients Objective observers reported a beneficial effect to morphine

(*Continued*)

Table I. (*Continued*).

Study	Type of intervention	Patients (N)	Diagnosis (cancer type)	Patient characteristics Age (median), gender	Inclusion criteria	Exclusion criteria	Duration of intervention	Design of trial, methodology	Description of the intervention effect by study authors
Charles, 2008	Nebulized hydromorphone vs. placebo (nebulized saline) vs. systemic hydromorphone	25	Lung 14p , breast 2p, renal 2p, mesothelioma 1p, prostate 1p	69 y (48–83) 9 women, 11 men	Age > 18 y; primary diagnosis of cancer with a clinical prognosis of at least 7 days, had to obtain Mini-Mental State Examination (MMSE) scores of at least 24 out of 30, who experiencing breathlessness.	Not reported	2 days	RCT, cross-over, double blind study, allocation generation - adequate	Only nebulized hydromorphone produced a rapid improvement in breathlessness that reached a magnitude considered to be clinically important
Clemens, 2009		46	Lung 19p , breast 11p, other 16p	Hypoxic pts: 66.5 y (40–90); Non-hypoxic pts: 70.5 y (40–86) 23 women, 23 men	Advanced, terminal cancer or other terminal incurable disease, dyspnea at rest. Normal cognitive status	Severe congestive heart failure, renal or hepatic failure	4 hours	Non-randomized comparative prospective trial	Opioids worked significantly better than oxygen in reducing the intensity of dyspnea
SC morphine vs. nebulized morphine									
Bruera, 2005	Group 1: day 1 s/c morphine + nebulized saline placebo, day 2 nebulized morphine + s/c placebo Group 2: day 1 nebulized morphine + placebo s/c, day 2 s/c morphine + nebulized saline placebo; duration of intervention: 2 d	12	Lung 7p , gastrointestinal 2p, other 3p	58 y (46–77) 4 women, 8 men	Dyspnea related to cancer, predominantly restrictive ventilation (no significant bronchospasm), resting dyspnea intensity of 3 (scale of 0–10), patients receiving regular or parenteral opioids, normal cognitive status	Any contra-indication to morphine, dyspnea related to acute complications (such as pneumonia, PE, CHF)	2 days	RCT, cross-over, double blind study, allocation generation: not reported, allocation concealment: not reported	No significant difference in dyspnea intensity On completion of study more patients preferred nebulized morphine
Morphine in different dosages									
Allard, 1999	25% vs. 50% of the 4-hourly regular morphine dose; Morphine administered s/c or oral; duration of intervention: 4 h	33	Lung 21p , breast 6p, other 6p	63.3 y 19 women, 14 men	Patients with persistent dyspnea at rest, already on opioids (oral or s/c), alert, not confused, no contraindication to opioids , no cognitive impairment on minimental test	Acute respiratory distress, > 3 rescue doses for breakthrough pain, receiving only "weak" opioids as codeine	4 hours	A randomized continuous sequential trial, double blind study, allocation generation: by a random list, allocation concealment: central randomization	25% of the equivalent 4-hourly dose of opioid equivalent to 50% with regard to VAS at 60 minutes. Both doses received an almost equal number of preferences by the patients

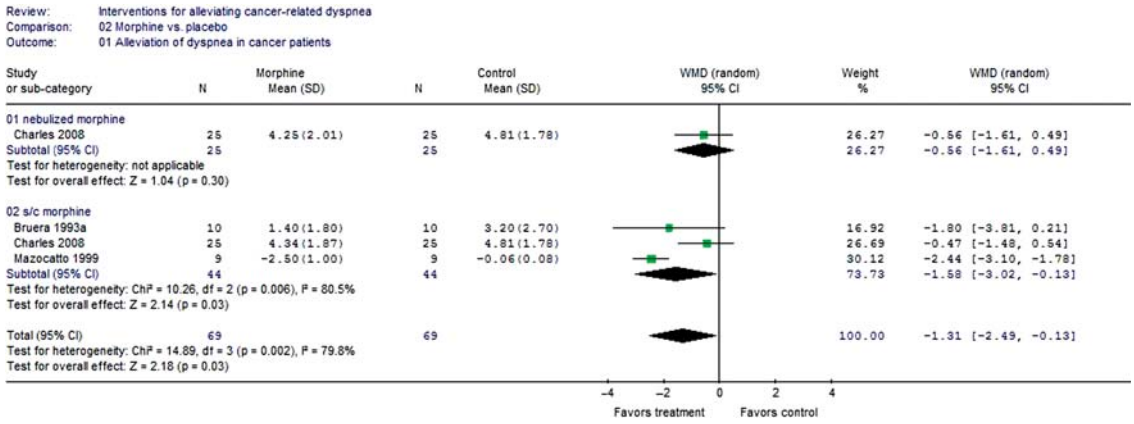

Figure 2. Meta-analysis of trials evaluating morphine versus placebo.

excluded chronic obstructive pulmonary disease patients [22,24,25]. Quality assessment of the included studies reflected poor quality. Two studies [21,23] had a high quality score. Meta-analysis of the six studies showed lack of benefit to oxygen to improve dyspnea, SMD − 0.3(95% CI − 1.06, 0,47) as demonstrated in Figure 3.

Adverse events. No adverse effects were reported in five of the trials. In the recent Abernathy et al. trial that assessed oxygen therapy compared with placebo, there were few adverse events without clinical significant difference between the two arms.

Benzodiazepines

Two studies compared midazolam versus morphine versus the combination of the two agents (Table III) [27,28]. In the first study morphine appeared more effective than midazolam at 24 hours though not statistically significant. The beneficial effect of morphine in controlling baseline levels of dyspnea may be improved with the addition of midazolam to the treatment [27). During the initial in-clinic phase of a recent study [28], dyspnea was alleviated by at least 50% both in both arms. During the ambulatory phase, midazolam was superior to morphine in controlling baseline and breakthrough dyspnea.

Furosemide

Two small studies evaluated nebulized furosemide versus placebo (Table III) [29,30]. Furosemide failed to improve dyspnea in both trials.

Discussion

The results of our updated systematic review and meta-analysis demonstrate a beneficial effect to opioids in alleviating cancer-related dyspnea, whereas oxygen does not confer a benefit. Opioids are helpful in both opioid-naïve and -tolerant patients, in whom dose escalation shows a better response [16,18]. In all of the studies that reported adverse events opioids did not increase somnolence or precipitated respiratory depression.

The included studies in our meta-analysis were crossover studies; nevertheless, paired analysis in a meta-analysis was not feasible. We therefore used the conservative method of pooling the data from the experimental and the control arms separately from the end of trial phase, and analyze these as if the trial was a parallel group trial of experimental arm versus control arm. The drawback of this method derives from the fact it may give rise to a unit-of-analysis error since confidence intervals are likely to be too wide and the trial might receive too little weight with the possible consequence that the intervention effect may be attenuated. Nevertheless, while this analysis is indeed conservative, the fact that the intervention (i.e. opioids) appears significantly more effective than the control further strengthens our results.

Variability exists between the studies as for the favorable route of administration. Whereas subcutaneous morphine appears to be beneficial in this analysis, the role of nebulized opioids remains to be elucidated. Potential role for nebulized opioids in the management of dyspnea due to various diseases had been implied in a former meta-analysis, though lacking a statistically significant benefit [8]. Two studies have implied that a higher dose of nebulized opioid may result in a better response [16,18]. Further studies are warranted to validate the benefit of nebulized opioids and to unravel whether the nebulization itself contributes to the therapeutic effect.

The term "opiophobia" had been coined 25 years ago in a narrative for describing the apprehension medical professionals and the public have with regards to opioid use [31]. The main concerns are related to the potential addiction to the drug, the correlation to respiratory depression and mostly to

Table II. Included Trials, Oxygen Use, Patient Characteristics and Study Design.

Study year	Type of intervention	Pts	Diagnosis (cancer type)	Patient characteristics (age (median), gender)	Duration of intervention	Inclusion criteria	Exclusion criteria	Design of trial, methodology	Description of the intervention effect by study authors
Abernathy, 2010 cancer patients only	Oxygen vs. air	31	lung cancer or lung mets	73 y (11) for oxygen group; 74 y (10) for air group	7 d	PaO2 more than 7.3 kPa, refractory dyspnea related to life-limiting illness received maximum treatment for underlying disease, reported dyspnea at rest or with negligible exertion , expected survival > 1 month	Met international eligibility guidelines for long-term oxygen therapy, had a history of hypercarbic respiratory failure with oxygen, had anemia (hemoglobin < 100 g/L), hypercarbia (PaCO2 > 6·7 kPa), or cognitive impairment (MMSE < 24/30), smoked, or had had a respiratory or cardiac event in the previous 7 days.	RCT, cross-over, double blind study, allocation generation and concealment–adequate	There was no statistically significant difference between the effect of air and oxygen on dyspnea
Phillip, 2006	Oxygen vs. air	51	Lung 28p, breast 8p, colorectal 4p, Comorbidity: COPD 11p	65 y (33–81) 31 men, 20 women	< 1 hour	Patients with terminal cancer, fully conscious, normal cognitive status, shortness of breath, VAS > 30 mm	Not reported	RCT, cross-over, double blind study, allocation generation: not reported, allocation concealment: not reported Inpatient	There was no statistically significant difference between the effect of air and oxygen on dyspnea
Bruera, 2003	Group 1: oxygen via cannula for 5 min then 6 min walking Group 2: air via cannula then 6 min walking	33	Lung 31p, lung mets 31p	64 y (41–79) 21 men, 12 women	< 1 hour	Patients with terminal cancer, fully conscious, normal cognitive status, SAT > 90%, Hb > 10	Acute respiratory event in the last 24 h or whom required oxygen during the last 4 weeks	RCT, cross-over, double blind study, allocation generation: computerized Outpatient	There was no statistically significant difference between the effect of air and oxygen on dyspnea

(*Continued*)

Table II. (*Continued*).

Study year	Type of intervention	Pts	Diagnosis (cancer type)	Patient characteristics (age (median), gender)	Duration of intervention	Inclusion criteria	Exclusion criteria	Design of trial, methodology	Description of the intervention effect by study authors
Booth, 1996	Oxygen vs. air	38	Lung 20p, lung mets 6p, pleural effusion 2p, lymphangitic spread 1p	71 y (54–90) 22 men, 16 women	<1 hour			RCT, cross-over, single blind study, allocation generation – adequate allocation concealment: not reported	No statistically significant difference between the effect of air and oxygen on dyspnea
Bruera, 1993	Oxygen vs. air (using Hills and Armitage test)	14	Lung 5p, lung mets 6p pleural effusion 2p lymphangiitic spread 1p	64 y (49–79) 8 men, 6 women	<1 hour	Patients with terminal cancer, fully conscious, normal cognitive status, O_2 saturation $<90\%$	COPD	RCT, double blind study, allocation generation: not reported, allocation concealment: not reported	Supplemental oxygen provided dyspnea relief for patients with dyspnea and hypoxia
Ahmedzai, 2004	Group 1: 6 min walk then medical air (78.9% N_2, 21.1% O_2) Group 2: 6 min walk then oxygen enriched air (72% N_2, 28% O_2)	12	Lung	72.5 y (58–78) 7 men, 5 women	<1 hour	Patients with lung cancer, dyspnea on exertion, life expectancy of at least 3 months	Pregnancy dyspnea at rest, history of psychiatric disabilities, Hb <10gr%, chemotherapy/ radiotherapy within 4 weeks of study	RCT, cross-over, double blind study, allocation generation: computerized Outpatient	No significant difference in relieving dyspnea between air and oxygen was noted in In patients dyspneic on exertion but not hypoxemic in rest

COPD, chronic obstructive pulmonary disease.

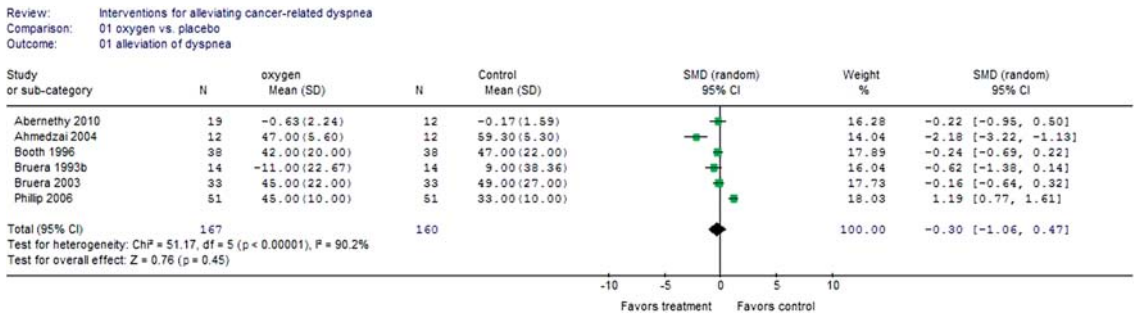

Figure 3. Meta-analysis of trials evaluating oxygen versus placebo.

the wide notion that opioids may shorten survival. Five studies evaluated the effect of opioids on survival. A systematic review found no significant effect on survival [32–37]. With regard to precipitating respiratory depression, in studies evaluating the administration of opioids for pain alleviation, the population at risk for respiratory depression was opioid-naïve patients only. In the setting of managing cancer-related dyspnea the majority of these terminally ill patients have been previously exposed to opioids.

The patient population included in the trials was heterogeneous. Two studies evaluated opioids in the setting of refractory dyspnea due to various etiologies and found no correlation between the baseline dyspnea degree and the response to opioids, although in one study there was a trend of an increased benefit in patients with low baseline dyspnea compared with severe baseline dyspnea [20,38].

The trials included in this meta-analysis enrolled both patients who were opioid-naïve and tolerant and degree of baseline dyspnea was not defined as a comparator.

Evaluation of dyspnea has been challenging due to the subjective nature of this symptom. The clinical significance of improvement observed by numerical scales as the VAS may be imprecise, nor is there a gold standard for a valid assessment of dyspnea improvement. Moreover, the differences between the study arms can be minor even when statistically significant. In some of the studies patient preference was presented. There is no methodology to appraise this subjective description, nor is there a definition to this preference. Nevertheless, given the unique nature of dyspnea, the patient preference may lend credence to a specific intervention. To note, in some of the studies, the qualitative patient's preference was stronger than the clinical significance observed by VAS score only.

Our meta-analysis found that oxygen provides no benefit in alleviating cancer-related dyspnea. According to a recent study by Abernathy moving either room air or oxygen near a nasal cannula can lead to improved symptoms while oxygen did not differ from room air. Oxygen is a commonly prescribed treatment for refractory dyspnea, and moreover, in hospitalized patients [39]. Oxygen saturation has not been a good predictor for response to oxygen [40] and therefore, the administration of oxygen may be beneficial on an individual basis, but once the patient does not experience improvement, continuation of oxygen should be reconsidered since it may be ineffective and may also carry adverse effects.

There is paucity of data regarding the role of other pharmacological interventions in alleviating cancer-related dyspnea. Benzodiazepines have been studied in two experimental settings [27,28] and data is conflicting; while in the first study midazolam had no superior effect to morphine, in a recent study, midazolam was more effective than morphine in controlling the breakthrough component of dyspnea during the ambulatory follow-up. This may be derived from the multifactorial nature of cancer-related dyspnea and the contribution of anxiety to its formation. Further studies are needed in order to reveal the role of benzodiazepines. Two small studies assessed nebulized furosemide found no beneficial effect to this treatment.

Limitations

Only a few randomized controlled trials were conducted addressing the question. The relative small number of patients included in each study contributes to the same drawback. Another limitation derives from the lack of dosage in the opioid trials and the inconsistency in the opioid type. Morphine is the predominant opioid in most of the studies; nevertheless, there is no evidence to support a specific dosing. There is no head to head comparison between morphine and hydromorphone to assess superiority of either agent. As for the RCTs evaluating oxygen there is an inconsistency between the studies in assessing hypoxemia, as the standard method of assessment varied between studies. Moreover, the measured outcome (dyspnea at rest or after walking), actual oxygen prescription (as needed, continuous, nocturnal, etc.) differed between studies.

Table III. Included Trials, Benzodiazepines and Furosemide Use, Patient Characteristics and Study Design.

Study	Type of intervention	Patients (N)	Diagnosis (cancer type)	Patient characteristics (age (median), gender)	Inclusion criteria	Exclusion criteria	Duration of intervention	Design of trial, methodology	Description of the intervention effect by study authors
Morphine vs. midazolam (any route)									
Navigante, 2006	Group 1: s/c morphine with midazolam rescue for breakthrough dyspnea Group 2: s/c midazolam with morphine rescue for breakthrough dyspnea; Group 3: Morphine plus midazolam with morphine rescue for breakthrough dyspnea	101	Lung 30p, breast 19p, gynecologic 14p, sarcomas 12p, ectal 7p, unknown primary 10p, other 9p	Morphine: 57.3 y 17 women, 18 men Midazolam: 57.8 y 20 women, 30 men Morphine + Midazolam: 56.9y 17 women, 16 men	Age > 18, documented terminal advanced cancer, life expectancy less than a week, MMSE > 23/30, severe dyspnea at rest, performance status 4	COPD with hypercapnia, non-compensated CHF, severe renal or hepatic failure, other uncontrolled symptoms that could require opioids	2 days	RCT, no blinding, allocation generation: by a random number generator, allocation concealment: not reported	Morphine non-significantly more effective than midazolam with regard to patients achieving dyspnea relief at 24 h Median on Borg scale 2 for the morphine, dyspnea relief 69%, Median on Borg scale 4 for the midazolam, dyspnea relief 46%, Median on Borg scale 3 for the morphine, dyspnea relief 92% Morphine combined with midazolam significantly more effective than Morphine or midazolam alone
Navigante, 2010	Group 1: oral morphine Group 2: oral midazolam	63	lung 16p , breast 15p, head and neck 6p, other 26p	Morphine: 55 y (30–80); Midazolam 59 y (36–82). Gender not reported	Age > 18, ambulatory with advanced cancer, MMSE > 23/30, severe dyspnea at rest, performance status ≤ 3	Active or uncontrolled COPD, CHF, severe renal or hepatic failure, SaO2 < 85%. Unstable patients who required immediate treatment or admission	4 days	RCT, cross-over, double blind study, allocation generation and concealment–adequate	Neither morphine nor midazolam affected the outcome and/or implementation of additional diagnostic and/or therapeutic interventions During the initial in-clinic phase, dyspnea was alleviated by at least 50% in all patients, whether they received morphine or midazolam During the ambulatory phase, midazolam was superior to morphine in controlling baseline and breakthrough dyspnea

(*Continued*)

Table III. (*Continued*).

Study	Type of intervention	Patients (N)	Diagnosis (cancer type)	Patient characteristics (age (median), gender)	Inclusion criteria	Exclusion criteria	Duration of intervention	Design of trial, methodology	Description of the intervention effect by study authors
Furosemide vs. placebo									
Wilcock, 2008	Nebulized furosemide vs. saline on a random order for 3 consecutive days. Breathlessness evaluation before and after arm exercise	15	Lung 7p, mesothelioma 2p, breast 2p, lung mets 4p	66 y (11) 7 men, 8 women	3 days	Primary or secondary lung cancer or mesothelioma with breathlessness on low levels of exertion or at rest (i.e. a score of >3 on the Dyspnea Exertion Scale	Breathlessness could be relieved by treatment such as drainage of a pleural effusion or blood transfusion. Radiotherapy or chemotherapy within 4 weeks, asthma, angina, heart failure	RCT, double blind study, allocation generation and concealment – adequate	No evidence of benefit from nebulized furosemide on any outcome measure BORG scale at maximum equivalent work load of 2.3 (1.5) for furosemide, 2.5 (1.4) for saline
Stone, 2002	Group 1: nebulized furosemide day1 (d1) and saline on d2 Group 2: saline on d1 then nebulized furosemide on d2	7	Lung 5p, breast 1p, lung mets 1p	72 y (63–80) 4 men, 3 women	2 days	Patients with terminal cancer, fully conscious, normal cognitive status	Asthma	RCT, double blind study, allocation generation: not reported, allocation concealment: not reported	No statistical difference between effect of furosemide and saline. There was a non-statistically significant trend of worsening in the furosemide group Mean VAS change of + 17 for furosemide, Mean VAS change of -25 for saline

Implications for practice

Opioids are the only evidence-based first line pharmacological treatment for cancer-related dyspnea, preferably given sub-cutaneously. The evidence for the benefit of nebulized opioids is inconclusive and warrants further evaluation.

Oxygen showed no benefit. Although it may benefit a subgroup of patients, identifying these patients is still challenging and requires careful selection of patients that improve after a short trial of oxygen while discontinue oxygen use in others. Benzodiazepines may offer an alternative to opioids though the evidence is limited. Furosemide should not be used for dyspnea in cancer patients with no other indication.

Implications for research

Future randomized controlled studies looking at the optimal dose of opioids and their optimal route of administration should be performed.

With regard to dosing, a recent study indicates that doses of morphine 10–20 mg/24 h had beneficial effect in the majority of patients [41].

Furthermore, one of the most complex aspects of dyspnea as compared to pain is the fact that the majority of patients develops intermittent dyspnea [42] which represents a major methodological challenge for studies on both oxygen and opioids and should be addressed as well.

Despite a recent RCT which was fully powered to assess the efficacy of oxygen [21], the issue of identifying the target population that would benefit from oxygen therapy remains unclear. Future studies should focus on defining standardized method of assessment of eligible patients (i.e. hypoxemic versus non hypoxemic), as well as exploring the rationale behind widely prescribing oxygen for this indication.

Further studies should be conducted to appraise benzodiazepines. Since the populations of the two studies presented here differ tremendously (performance status 4 versus lower than 3) it is unclear which population would benefit most from benzodiazepines – the terminally ill or by contrast the ambulatory patients with a better performance status.

Studies should distinguish between lung cancer patients and patients with other causes for dyspnea since the response to pharmacological interventions may differ. Since palliative trials address a heterogeneous population, it is recommended to separate the patients upon their expected survival and, moreover, to provide the survival data.

Opioids have been shown to be safe and effective when used for managing symptoms as pain and dyspnea in terminally-ill patients with advanced cancer. Nevertheless, despite the established evidence, the providers' perception is still hard to shift. Physicians should be encouraged to use opioids – not only as a treatment for pain but also for cancer-related dyspnea.

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Notice of Correction

The version of this article published online ahead of print on 30 Aug 2012 contained an error on page 9. The figure legend to Figure 3 should have read "Meta-analysis of trials evaluating oxygen versus placebo". The error has been corrected for this version.