Interventions for Dyspnea in Patients with Advanced Cancer

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

The Patient-Centered Outcomes Research Institute (PCORI) was established to fund research that can help patients and those who care for them make better informed decisions about the health care choices they face every day. PCORI partnered with AHRQ to help fulfill PCORI’s authorizing mandate to engage in evidence synthesis and make information from comparative effectiveness research more available to patients and providers. PCORI identifies topics for review based on broad stakeholder interest. After identifying specific topics, multistakeholder virtual workshops are held by PCORI to inform the individual research protocols.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

<to be listed in the Final Report>

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows:

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Interventions for Dyspnea in Patients with Advanced Cancer

Structured Abstract

Objectives. To assess benefits and harms of non-pharmacologic and pharmacologic interventions for dyspnea in adults with advanced cancer.

Data sources. We searched PubMed®, Embase®, CINAHL, ISI Web of Science, and the Cochrane Central Register of Controlled Trials through early September 2019.

Review methods. We included randomized controlled trials (RCTs) and observational studies with a comparison group evaluating benefits and/or harms and cohort studies reporting harms. Two reviewers independently screened search results, serially abstracted data, assessed risk of bias and graded strength of evidence (SOE) for key outcomes: dyspnea, anxiety, health-related quality of life (HRQOL) and functional capacity. We performed meta-analyses when possible and calculated standardized mean differences (SMDs).

Results. We included 39 RCTs and 2 retrospective cohort studies (3679 patients). The most commonly reported type of cancer was lung cancer or mesothelioma. The baseline level of dyspnea varied in severity and measurement method. Several non-pharmacological interventions were effective for dyspnea, including fans [SMD -1.23 (95% CI -1.74 to -0.71)] (SOE: Moderate), non-invasive positive pressure ventilation (NPPV) (estimated slope difference -0.58 (95% CI -0.92 to -0.23) and acupuncture/ acupressure/ reflexology [SMD 0.56 (95% CI -0.87 to -0.26)] (SOE: Low). Multicomponent interventions (behavioral/ psychoeducational combined with activity/ rehabilitation and/or complementary and alternative medicine) were effective for improving dyspnea and HRQOL. Opioids were not more effective than placebo (SOE: moderate) for improving dyspnea [SMD -0.06 (95% CI, -0.41 to 0.3)] or functional capacity (SOE: moderate); most studies were of exertional dyspnea. Different doses or routes of administration of opioids did not affect dyspnea (SOE: Low). Anxiolytics were not more effective than placebo for dyspnea or anxiety (SOE: low). Evidence for other pharmacological interventions was limited. Opioids, NPPV, and activity and rehabilitation interventions had some harms compared to usual care.

Conclusions. Some non-pharmacological interventions, including fans, acupuncture/ acupressure/ reflexology, multicomponent interventions, and NPPV were effective for dyspnea in advanced cancer. Evidence did not support opioids or other pharmacological interventions, although studies had limitations. More research is needed on when opioids may be useful in this population.
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Evidence Summary

Main Points

For patients with advanced cancer:

- Airflow and cooling interventions (fans) were more effective for improving dyspnea compared to usual care or sham.
- Non-invasive positive pressure ventilation (NPPV) with bi-level positive airway pressure (BPAP) was more effective than supplemental oxygen for improving dyspnea.
- Acupuncture/acupressure/reflexology were more effective than usual care or sham for improving dyspnea.
- Neither behavioral/psychoeducational interventions alone and activity/rehabilitation interventions alone were more effective than usual care for improving dyspnea. However, multicomponent interventions that combined these, with or without complementary and alternative medicine interventions, were more effective than usual care for improving dyspnea.
- Opioids were not more effective than placebo or anxiolytics for improving dyspnea or functional capacity; most of these studies in advanced cancer were of exertional dyspnea. Studies on opioids showed no differences in effectiveness between different doses or routes of administration for improving dyspnea.
- Anxiolytics were not more effective than placebo for improving dyspnea.
- Both non-pharmacological and pharmacological interventions led to adverse event-related dropouts in only a small percentage of patients.

Background and Purpose

Dyspnea, defined as difficulty breathing or shortness of breath, is frequent in advanced cancer\(^1\) and often debilitating. Both chronic and episodic dyspnea can reduce ability to function and participate in desired activities\(^2\) and can be distressing for caregivers and patients. When treatment of the primary cause or comorbidities does not fully relieve symptoms or is not possible, non-pharmacological and pharmacological interventions can help improve symptoms.

This systematic review comprehensively reviews data to help the American Society for Clinical Oncology prepare a clinical practice guideline on comparative benefits and harms of non-pharmacological and pharmacological interventions for management of dyspnea in adults with advanced cancer.

Methods

We followed the Agency for Healthcare Research and Quality’s (AHRQ’s) Methods Guide
Results

We describe the key findings below; the full report contains the results for all the outcomes.

**KQ1. What are the comparative benefits of non-pharmacological interventions (either alone or in combination) for improving dyspnea in patients with advanced cancer?**

We identified 24 randomized controlled trials (RCTs) (2063 patients).

**Respiratory interventions (8 RCTs)**
- Airflow and cooling interventions (2 RCTs, n=70) (fans) were effective for improving dyspnea compared to usual care or sham [Meta-analysis: standardized mean difference (SMD), -1.23; 95% CI -1.74 to -0.71, favoring the fan arm] (Strength of evidence (SOE): Moderate).
- Compressed air and supplemental oxygen (4 RCTs, n=136) did not differ for improving dyspnea (SOE: Low).
- Non-invasive positive pressure ventilation (NPPV) with bi-level positive airway pressure (BPAP) (2 RCTs, n=230), was more effective than supplemental oxygen for improving dyspnea [estimated slope difference, -0.58; 95% CI, -0.92 to -0.23, favoring BPAP] (SOE: Low). BPAP and high flow oxygen did not differ for improving dyspnea (SOE: Low).

**Behavioral/ psychoeducational interventions (3 RCTs)**
- Behavioral/psychoeducational interventions and usual care did not differ for improving dyspnea or health-related quality of life (SOE: Low).

**Activity/ Rehabilitation (4 RCTs)**
- Activity/rehabilitation interventions did not improve dyspnea, or health-related quality of life, but did improve functional capacity, more than usual care (SOE: Low).

**Complementary and alternative medicine (4 RCTs)**
- Acupuncture/acupressure/reflexology were more effective than usual care or sham at improving dyspnea and health-related quality of life (SOE: Low).

**Multicomponent interventions (behavioral/ psychoeducational combined with activity/ rehabilitation and/or complementary and alternative medicine) (5 RCTs)**
- Multicomponent interventions were more effective for improving dyspnea compared with usual care (SOE: Low).

**KQ2. What are the comparative benefits of pharmacological interventions (either alone or in combination) for improving dyspnea in patients with advanced cancer?**

We identified 14 RCTs and 1 retrospective study (1192 patients).
- Opioids were not more effective than placebo (SOE: moderate) for improving dyspnea [Meta-analysis: SMD, -0.06; 95% CI, -0.41 to 0.3] or functional capacity (most studies were of exertional dyspnea), and not more effective than anxiolytics for improving dyspnea (SOE: Low).
- Studies showed no difference in effectiveness between different doses or routes of administration of opioids for improving dyspnea (SOE: Low).
- Anxiolytics were not more effective than placebo for improving dyspnea (SOE: Low).
- Evidence for other pharmacological interventions was limited.

KQ3. What are the comparative benefits of non-pharmacological, pharmacological, and multimodal interventions for improving dyspnea in patients with advanced cancer?

The evidence was insufficient to draw conclusions (1 RCT, 173 patients).

KQ4. What are the harms of non-pharmacological and pharmacological interventions for improving dyspnea in patients with advanced cancer?

Non-pharmacological Interventions
- NPPV was associated with equipment discomfort/distress in some participants, leading to dropouts among some participants.
- Few studies reported harms, which limited our ability to draw conclusions.

Pharmacological Interventions
- Corticosteroids had lower rates of drowsiness compared with placebo or opioids.
- Opioids had higher rates of constipation compared with steroids.
- Adverse effects led to dropouts among a small percentage of patients for all types of pharmacological interventions.

Nonpharmacological Compared with Pharmacological
The evidence was insufficient to draw any conclusions.

Strengths and Limitations

We identified a large number of studies evaluating a variety of non-pharmacological and pharmacological interventions for different types of dyspnea in various settings for advanced cancer. However, sample sizes were generally small, followup was short term, most studies only used visual analog scales for measuring dyspnea, study attrition was high given the severity of illness, and the heterogeneity of settings and intervention types limited conclusions. Although none of the evidence supported the effectiveness of opioids for dyspnea, all but one of the
placebo-controlled studies were in short-term exertional dyspnea. Most studies included patients with lung cancer and chronic obstructive pulmonary disease, but we were unable to perform subgroup analyses.

Implications and Conclusions

In conclusion, a variety of non-pharmacological interventions, including fans, NPPV, acupuncture/acupressure/reflexology, and multicomponent interventions (behavioral and psychoeducational combined with activity and rehabilitation and/or complementary and alternative) were effective for improving dyspnea in patients with advanced cancer. Opioids and anxiolytics were not effective, although studies were limited, and few studies evaluated other pharmacologic interventions. Clinical practice guidelines that recommend opioids for dyspnea are based mainly on results from short-term studies of opioid-naïve patients with chronic obstructive pulmonary disease. Well-designed studies are needed to determine when opioids may be effective in various advanced cancer populations and settings.

References


Introduction

Background

Dyspnea, defined as difficulty breathing or shortness of breath, is frequent in patients with advanced cancer and often debilitating. Chronic, episodic, or exertional dyspnea can reduce quality of life, functional status, and the ability to participate in desired activities. It can be distressing for patients and caregivers. Dyspnea and anxiety are often interrelated: anxiety may masquerade as dyspnea, and dyspnea or fear of dyspnea is often anxiety-provoking. Objective findings (such as oxygen saturation or respiratory rate) are frequently monitored in clinical practice, but often do not correlate with symptoms. When treatment of the clinical conditions causing dyspnea does not fully relieve symptoms or is not an option, non-pharmacologic and pharmacologic palliative measures can be tried to help improve symptoms. Ideally, the outcome of dyspnea for intervention studies should be a comprehensive assessment including not only dyspnea severity, but also impact on function, quality of life, and anxiety.

The decisional dilemma for clinicians, patients, and caregivers is, “Are the benefits of non-pharmacological and/or pharmacological interventions likely to exceed potential harms for patients with dyspnea due to advanced cancer?” A variety of non-pharmacological and pharmacological treatments have been evaluated for management of dyspnea. These interventions also may be combined with each other in multimodal interventions. An overview of interventions is briefly presented below.

Non-pharmacological Treatment

Non-pharmacological treatments potentially helpful for dyspnea include respiratory, behavioral and psychoeducational, activity and rehabilitation, and complementary and alternative medicine interventions. Respiratory interventions can include cooling through fan therapy, water spray, supplemental oxygen, compressed air, or noninvasive positive-pressure ventilation (NPPV). Various behavioral or psychoeducational interventions may be used, including cognitive behavioral therapy and relaxation or distraction exercises. Activity and rehabilitation interventions may include breathing exercises, pulmonary rehabilitation, or physical interventions such as mobility aids or exercise. Complementary and alternative medicine interventions include acupuncture, acupressure, meditation, and music therapy.

Pharmacological Treatment

Pharmacological treatments for dyspnea in advanced cancer may include medications treating underlying pathophysiology, such as bronchodilators, diuretics, or corticosteroids, or medications treating the symptom, such as opioids, phenothiazines, atypical antipsychotics, nonsteroidal anti-inflammatory agents, or lidocaine. Anxiolytics could help treat the symptom of dyspnea directly or indirectly (by reducing associated anxiety).

Other types of interventions may help to reduce dyspnea but are outside the scope of this review because they target specific indications. These include interventional procedures, such as: stenting, thoracentesis, and pleural catheters for bronchial obstruction or pleural effusions; anticancer treatments, such as chemotherapy or radiation therapy; and interventions for closely associated symptoms such as cough or secretions. Other symptoms common in advanced cancer, such as pain, may interact with dyspnea, but are outside the scope of this review. Guidelines support comprehensive symptom assessment and treatment as consistent with patient preferences for underlying and contributing causes of dyspnea, such as anemia, pneumonia,
pneumonitis, pulmonary embolism, bronchial obstruction, and pleural effusions.\textsuperscript{11}

**Purpose of the Review**

This systematic review will provide a comprehensive review of current evidence to help the American Society of Clinical Oncology (ASCO) to prepare a clinical practice guideline on comparative benefits and harms of pharmacological and non-pharmacological interventions for the management of dyspnea in adults with advanced cancer.
Methods

Review Approach

We followed the methods outlined in the Agency for Healthcare Research and Quality’s (AHRQ’s) Methods Guide for Effectiveness and Comparative Effectiveness Reviews. This systematic review also reports in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA).12

The topic of this systematic review was developed by the Patient Centered Outcomes Research Institute (PCORI) in consultation with AHRQ. We recruited a Technical Expert Panel (TEP) to review a draft of the protocol. The TEP included representatives from palliative care, pulmonary medicine, pharmacology, and nursing, as well as a patient advocate. With the feedback from the TEP and the AHRQ and professional society representatives, we finalized the protocol and posted it on the AHRQ Effective Health Care Program’s Web site (www.effectivehealthcare.ahrq.gov).

Key Questions (KQ)

1. What are the comparative benefits of non-pharmacological interventions (either alone or in combination) for improving dyspnea in patients with advanced cancer?
2. What are the comparative benefits of pharmacological interventions (either alone or in combination) for improving dyspnea in patients with advanced cancer?
3. What are the comparative benefits of non-pharmacological, pharmacological, and multimodal interventions for improving dyspnea in patients with advanced cancer?
4. What are the harms of non-pharmacological and pharmacological interventions for improving dyspnea in patients with advanced cancer?

Analytic Framework

Figure 1 displays the analytic framework for addressing the Key Questions.
Figure 1. Analytic framework for evaluating interventions for dyspnea in patients with advanced cancer

(KQ 1, 2, 3)

- Non-pharmacological interventions
- Pharmacological interventions

(KQ 1, 2, 3, 4)

Patient- or caregiver-reported, or observational symptom-related outcomes (KQ 1-3)
- Dyspnea
- Anxiety
- Functional status
- Health-related quality of life

Clinical or utilization health outcomes (KQ 1-4)
- Respiratory rate
- Oxygen or carbon dioxide/bicarbonate levels
- Heart rate
- Blood pressure
- Objective measure of functional capacity
- Level of sedation
- Utilization outcomes linked to dyspnea

KQ 1 - 4: Patients (age ≥ 18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea

Patient-centered adverse effects of dyspnea treatments
- Central nervous system (cognitive changes, dizziness, drowsiness, fatigue, headache, respiratory depression)
- Gastrointestinal (constipation, nausea, vomiting)
- Pruritus
- Urinary retention, dry mouth
- Opioid use disorder
- Discomfort or distress from equipment, death, dropouts

KQ = Key Question
Study Selection

We searched the following databases for primary studies through early September 2019: PubMed, Embase®, CINAHL, ISI Web of Science, and the Cochrane Central Register of Controlled Trials. Study selection was based on predefined eligibility criteria within the framework shown in Table 1, which lists our inclusion and exclusion criteria in terms of the Population, Intervention, Comparison, Outcomes, Timing, Setting and Study (PICOTS). Full details on the search strategy and eligibility criteria are in the Methods Appendix.

Two reviewers independently screened each abstract. Both reviewers needed to agree that an article met at least one of the exclusion criteria to be excluded (see Table 1). We tracked and resolved differences between reviewers through consensus adjudication. Articles promoted on the basis of the abstract screen underwent another screen using the same process.

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KQ = key question, RCT = randomized controlled trial
*Please see figure 1 and Methods appendix for the complete list of interventions.
Data Extraction and Risk of Bias Assessment

Paired investigators abstracted data sequentially, and independently assessed risk of bias for individual studies. We used the Cochrane Risk of Bias Tool, Version 2, for assessing the risk of bias of randomized controlled trials (RCTs). For non-randomized studies of treatment interventions, we used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I tool). Overall risk of bias for each study was classified as low risk of bias, some concerns, and high risk of bias. Differences between reviewers were resolved through consensus. Details on the data extraction are in the Methods Appendix.

Data Synthesis and Analysis

We organized the report by Key Question and, then, by intervention and outcome. We conducted qualitative synthesis for each Key Question. We created detailed evidence tables containing all information extracted from eligible studies. We conducted meta-analyses when there were sufficient data (at least two studies) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, intervention, and outcome measures).

For continuous outcomes, we calculated a pooled mean between group difference by using a random-effects model with the DerSimonian and Laird method. Patient reported and clinical scales were standardized by estimating the standardized mean difference using the Cohen d method. When possible, we calculated a pooled standardized mean d. For studies that did not include variability measures, the standard deviation of change in mean was calculated using a correlation coefficient of 0.5, in accordance with methods provided in Fu et al (2013). We used Cohen’s classification to categorize effect sizes as small, medium or large.

In a situation where dichotomous outcomes were presented, we calculated a pooled effect estimate of the relative risk (RR) between the trial arms of RCTs by using a random-effects model with the DerSimonian and Laird method. For sparse data meta-analysis, we employed the Peto odds ratio method when event rates were less than 1 percent. When event rates were between 5-10%, there were substantial differences between the size of two arms, or effect size was large, dichotomous data was meta-analyzed using the Mantel-Haenszel method without continuity correction. Dichotomous data with zero values in both arms were not included in meta-analyses. Studies with no events in both groups were qualitatively summarized by providing information on the confidence intervals for the proportion of events in each arm.

We considered a 10 mm difference on a 100 mm VAS (visual analog scale) as clinically significant based on available data (see Methods Appendix for more details). We used STATA statistical software (Intercooled, version 14, StataCorp, College Station, TX) for all meta-analyses. We qualitatively summarized studies that were not amenable to pooling.

Grading the Strength of the Body of Evidence

We graded the strength of evidence using the grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews. We applied evidence grades to the bodies of evidence about each comparison for the outcomes we classified during protocol development as the critical outcomes, including health-related quality of life, dyspnea, anxiety, and functional capacity. We assessed the limitations to individual study quality (using individual risk of bias assessments), consistency, directness, precision, and reporting bias. We classified the strength of evidence into four categories: high grade, moderate grade, low grade, and insufficient grade.
Conclusions based on RCTs started with a high grade which could be downgraded based on the assessment on the five domains. Details regarding the domains assessed, the processes for determining the grades, and the definitions of each grade are listed in the Methods Appendix.
Results

Search Results

We retrieved 7171 unique citations (Results Appendix, Figure 1). After screening abstracts and full text, we included 41 studies.

Of the eligible studies, 24 RCTs addressed the benefits and harms of non-pharmacological interventions, 16 studies (14 RCTs and 2 retrospective studies) addressed the benefits and harms of pharmacological interventions, and one RCT addressed the benefits and harms of non-pharmacological, pharmacological, and multimodal interventions. We list the number of studies by type of outcome assessed in Table 2.

Table 2. List of included studies by outcomes

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Total number of studies</th>
<th>Patient- or caregiver-reported, or observational symptom-related outcomes</th>
<th>Clinical or utilization health outcomes</th>
<th>Patient-centered adverse effects of dyspnea treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits and harms of non-pharmacological interventions [KQ1 and 4]</td>
<td>24 (24 RCTs)</td>
<td>24 (24 RCTs)</td>
<td>12 (12 RCTs)</td>
<td>4 (4 RCTs)</td>
</tr>
<tr>
<td>Benefits and harms of pharmacological interventions [KQ2 and KQ4]</td>
<td>16 (14 RCTs, 2 retrospective studies)</td>
<td>15 (14 RCTs, 1 retrospective study)</td>
<td>10 (14 RCTs, 1 retrospective study)</td>
<td>14 (12 RCTs, 2 retrospective studies)</td>
</tr>
<tr>
<td>Benefits and harms of non-pharmacological, pharmacological, and multimodal [KQ3 and KQ4]</td>
<td>1 (1 RCT)</td>
<td>1 (1 RCT)</td>
<td>NR</td>
<td>1 (1 RCT)</td>
</tr>
</tbody>
</table>

KQ = key question; NR = not reported; RCT = randomized controlled trial
KQ1. What are the comparative benefits of non-pharmacological interventions (either alone or in combination) for improving dyspnea in patients with advanced cancer?

Key points

Dyspnea

- Airflow and cooling interventions (e.g., fans) were effective for improving dyspnea compared to usual care or sham intervention in patients with advanced cancer (Strength of evidence (SOE): Moderate).
- NPPV, such as Bi-level Positive Airway Pressure (BPAP), was more effective than 4-5 L/minute of supplemental oxygen at improving dyspnea in patients with advanced cancer (SOE: Low).
- Behavioral/psychoeducational interventions alone and activity/rehabilitation interventions alone were no more effective than usual care for improving dyspnea, or health-related quality of life in patients with advanced cancer (SOE: Low). We were unable to draw conclusions for comparisons between different types of activity/rehabilitation interventions (SOE: Insufficient).
- Multicomponent interventions which combined behavioral/psychoeducational and activity/rehabilitation interventions, with or without complementary and alternative medicine interventions were effective for improving dyspnea compared to usual care in patients with advanced cancer (SOE: Low). In addition, the multicomponent interventions (without additional complementary and alternative medicine interventions) were also effective at improving anxiety when compared with usual care in patients with advanced cancer (SOE: Low).
- Complementary and alternative medicine interventions (acupuncture, acupressure, reflexology) were more effective than usual care or sham procedures at improving dyspnea and health-related quality of life in patients with advanced cancer (SOE: Low). We were unable to draw conclusions for music therapy (SOE: Insufficient).

Twenty-four RCTs addressed the benefits of non-pharmacological interventions for managing dyspnea in patients with advanced cancer. The characteristics of the studies, participants, and interventions are listed in Appendix D-Evidence Tables 1, 4, 7, 8, and 13.

We present results by the type of intervention - respiratory (8 RCTs), behavioral and psychoeducational (3 RCTs), activity and rehabilitation (4 RCTs), complementary and alternative medicine (4 RCTs), and multicomponent (5 RCTs). See Appendix D, Evidence Tables 16 through 28, for details of the outcome data.

The summary of key findings and SOE for the key outcomes are presented in Tables 3 and 4. Wherever it says “calculated” in the results, those are the calculations done by us.
Table 3. Summary of key findings for the effects of non-pharmacological interventions on dyspnea in patients with advanced cancer

<table>
<thead>
<tr>
<th>Intervention Description</th>
<th>Evidence of Difference</th>
<th>Strength of Evidence</th>
<th>Total Population Size (n) and Study Number</th>
<th>Key Findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory interventions:</strong> Airflow/cooling vs. usual care or placebo</td>
<td>Improvement</td>
<td>Moderate</td>
<td>2 RCTs n = 70</td>
<td>These interventions yielded a statistically significant improvement in dyspnea in the intervention arm, compared to the control arm. On meta-analyses, the SMD was -1.23 (95% CI, -1.74 to -0.71, I-squared = 0.0%, p = 0.76) favoring the fan arm.</td>
<td>Fans are effective for improving dyspnea</td>
</tr>
<tr>
<td><strong>Respiratory interventions:</strong> Compressed air vs. oxygen</td>
<td>Equivalence</td>
<td>Low</td>
<td>4 RCTs n = 136</td>
<td>3 RCTs reported no statistically significant between group differences. One RCT reported improvement in the oxygen arm compared with compressed air arm.</td>
<td>Compressed air and supplemental oxygen did not differ for improving dyspnea</td>
</tr>
<tr>
<td><strong>Respiratory interventions:</strong> NPPV vs. high flow oxygen</td>
<td>Equivalence</td>
<td>Low</td>
<td>1 RCT n = 30</td>
<td>1 RCT reported no between group differences between BPAP and high flow oxygen. The standardized mean differences were 0.37 (95% CI, -0.34 to 1.10) for numeric rating scale, and 0.18 (95% CI, -0.90 to 0.53) for the modified Borg scale.</td>
<td>BPAP and high flow oxygen did not differ for improving dyspnea</td>
</tr>
<tr>
<td><strong>Respiratory interventions:</strong> NPPV vs. supplemental oxygen</td>
<td>Improvement</td>
<td>Low</td>
<td>1 RCT n = 200</td>
<td>BPAP yielded a statistically significant improvement in dyspnea compared with supplemental oxygen (p=0.0012).</td>
<td>BPAP is effective for improving dyspnea compared to supplemental oxygen</td>
</tr>
<tr>
<td><strong>Behavioral/psychoeducational interventions vs. usual care</strong></td>
<td>Equivalence</td>
<td>Low</td>
<td>3 RCTs n = 745</td>
<td>2 RCTs reported no statistically significant between group differences. One RCT reported improvement in the intervention arm compared to the control arm (p=0.03).</td>
<td>No clinically important improvement in dyspnea</td>
</tr>
<tr>
<td>Intervention</td>
<td>Evidence of difference</td>
<td>Strength of evidence</td>
<td>Total population size (n) and study number</td>
<td>Key findings</td>
<td>Conclusion</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------------------</td>
<td>----------------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acupuncture/ acupressure/ reflexology vs. placebo intervention or usual care or both</td>
<td>Improvement</td>
<td>Low</td>
<td>3 RCTs n = 391</td>
<td>2 RCTs reported a statistically significant between group differences favoring the intervention arm. One RCT reported no improvement in the intervention arm compared with the control arm.</td>
<td>Acupuncture/acupressure/reflexology are more effective for improving dyspnea than usual care or sham procedures</td>
</tr>
<tr>
<td>Music therapy vs. usual care</td>
<td>No conclusion drawn</td>
<td>Insufficient</td>
<td>1 RCT n = 40</td>
<td>Statistically significant improvement in dyspnea in the music therapy group but not in the placebo group. Between group differences and effect sizes were not reported.</td>
<td>NA</td>
</tr>
<tr>
<td>Activity/ rehabilitation interventions vs. activity/ rehabilitation interventions or usual care</td>
<td>Equivalence</td>
<td>Low</td>
<td>4 RCTs n = 123</td>
<td>3 RCTs reported no statistically significant between group differences. One RCT reported improvement in the intervention arm compared with the control arm.</td>
<td>There were no differences between different activity/rehabilitation interventions or usual care for improving dyspnea</td>
</tr>
<tr>
<td>Multicomponent combined behavioral/psychoeducational and activity/ rehabilitation Interventions, vs. usual care</td>
<td>Improvement</td>
<td>Low</td>
<td>2 RCTs n = 160</td>
<td>Significant improvement in dyspnea in the intervention arm.</td>
<td>Multicomponent combined behavioral/psychoeducational and activity/rehabilitation Interventions were more effective for improving dyspnea than usual care</td>
</tr>
<tr>
<td>Multicomponent combined behavioral/psychoeducational, activity/ rehabilitation and complementary and alternative medicine interventions, vs. usual care</td>
<td>Improvement</td>
<td>Low</td>
<td>2 RCTs n = 168</td>
<td>Significant improvement in dyspnea in the intervention arm. The mean between group difference was 5.19 (95% CI, 0.62 to 9.75), and -1.29 (95% CI, -2.57 to -0.005).</td>
<td>Multicomponent combined behavioral/psychoeducational, activity/rehabilitation and complementary and alternative medicine interventions were more effective for improving dyspnea than usual care</td>
</tr>
</tbody>
</table>
### Table 4. Summary of key findings for the effects of non-pharmacological interventions on anxiety, functional capacity and health-related quality of life in patients with advanced cancer

| Multicomponent combined behavioral/psychoeducational and complementary and alternative Medicine interventions vs. usual care |
|---|---|---|---|---|
| Evidence of difference | Strength of evidence | Total population size (n) and study number | Key findings | Conclusion |
| No conclusion drawn | Insufficient | 1 RCT n = 50 | No statistically significant difference between arms. | NA |

SMD= standardized mean difference; RCT=randomized controlled trial ; NPPV= non-invasive positive pressure ventilation; BPAP= bi-level positive airway pressure; vs.= versus. NA = not applicable
Blue dot size corresponds to number of participants in the study.

**Anxiety**

Respiratory interventions: Airflow/cooling vs. usual care or placebo
- Evidence of difference: No conclusion drawn
- Strength of evidence: Insufficient
- Total population size (n) and study number: 1 RCT n = 40
- Key findings: No statistically significant between group differences. The SMD was -0.11 (95% CI, 0.73 to 0.50).
- Conclusion: NA

Acupuncture/acupressure/reflexology vs. placebo intervention or usual care or both
- Evidence of difference: No conclusion drawn
- Strength of evidence: Insufficient
- Total population size (n) and study number: 1 RCT n = 286
- Key findings: No statistically significant between group differences.
- Conclusion: NA

Music therapy vs. usual care
- Evidence of difference: No conclusion drawn
- Strength of evidence: Insufficient
- Total population size (n) and study number: 1 RCT n = 40
- Key findings: Statistically significant improvement in anxiety in the music therapy group but not in the placebo group. Between group differences and effect sizes were not reported.
- Conclusion: NA
<table>
<thead>
<tr>
<th>Activity and rehabilitation interventions vs. activity and rehabilitation interventions or usual care</th>
<th>Evidence of difference</th>
<th>Strength of evidence</th>
<th>Total population size (n) and study number</th>
<th>Key findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No conclusion drawn</td>
<td>?</td>
<td>2 RCTs n = 80</td>
<td>1 RCT reported no statistically significant between group differences. One RCT reported improvement in intervention arm compared to control arm.</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multicomponent combined behavioral/ psychoeducational and activity/ rehabilitation Interventions vs. usual care</th>
<th>Improvement</th>
<th>Low</th>
<th>2 RCTs n = 160</th>
<th>1 RCT reported no statistically significant between group differences. One RCT reported improvement in intervention arm compared to control arm.</th>
<th>Multicomponent combined behavioral/ psychoeducational, activity/ rehabilitation and alternative medicine interventions were more effective at improving anxiety compared to usual care</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Multicomponent combined behavioral/ psychoeducational, activity/ rehabilitation and complementary and alternative medicine Interventions vs. usual care</th>
<th>Equivalence</th>
<th>Low</th>
<th>2 RCTs n = 168</th>
<th>Meta-analysis of 2 RCTs showed no statistically significant difference between arms. The SMD was -0.20 (95 CI: -0.12 to 0.52), (I-squared = 0.0%, p = 0.42).</th>
<th>Multicomponent combined behavioral/ psychoeducational, activity/ rehabilitation and complementary and alternative medicine interventions were not effective for improving anxiety compared to usual care</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Combined Behavioral/ Psychoeducational and Complementary and Alternative Medicine Interventions vs. usual care</th>
<th>No conclusion drawn</th>
<th>Insufficient</th>
<th>1 RCT n = 50</th>
<th>No statistically significant difference between arms.</th>
<th>NA</th>
</tr>
</thead>
</table>

<p>| Functional capacity |</p>
<table>
<thead>
<tr>
<th>Evidence of difference</th>
<th>Strength of evidence</th>
<th>Total population size (n) and study number</th>
<th>Key findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory interventions: Compressed air vs. oxygen</strong></td>
<td>![No conclusion drawn]</td>
<td>![Insufficient]</td>
<td>![1 RCT n = 33]</td>
<td>No statistically significant between group differences. The SMD was -0.11 (95% CI, 0-0.73 to 0.50).</td>
</tr>
<tr>
<td><strong>Acupuncture/ acupressure/ reflexology vs. placebo intervention or usual care or both</strong></td>
<td>![No conclusion drawn]</td>
<td>![Insufficient]</td>
<td>![1 RCT n = 60]</td>
<td>No difference</td>
</tr>
<tr>
<td><strong>Activity/ rehabilitation interventions vs. activity/ rehabilitation interventions or usual care</strong></td>
<td>![No conclusion drawn]</td>
<td>![Insufficient]</td>
<td>![2 RCTs n = 53]</td>
<td>2 RCTs reported a statistically significant between group differences favoring the intervention arm.</td>
</tr>
<tr>
<td><strong>Health-related quality of life</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Behavioral/ psychoeducational interventions vs. usual care</strong></td>
<td>![Equivalence]</td>
<td>![Low]</td>
<td>![3 RCTs n = 745]</td>
<td>No statistically significant between group differences. Behavioral/ psychoeducational interventions did not improve health-related quality of life compared to usual care</td>
</tr>
<tr>
<td>Intervention Type</td>
<td>Evidence of difference</td>
<td>Strength of evidence</td>
<td>Total population size (n) and study number</td>
<td>Key findings</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>----------------------</td>
<td>-------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acupuncture/ acupressure/ reflexology vs. placebo intervention or usual care or both</td>
<td>Improvement</td>
<td>Low</td>
<td>2 RCTs n = 346</td>
<td>On meta-analysis, the SMD was -0.56 (95% CI: -0.87 to -0.26), (I^2) squared = 98.5%, (p = 0.000), favoring the intervention arm. Heterogeneity was high.</td>
</tr>
<tr>
<td>Activity/ rehabilitation interventions vs. activity/ rehabilitation interventions or usual care</td>
<td>Equivalence</td>
<td>Low</td>
<td>4 RCTs n = 123</td>
<td>3 RCTs reported no statistically significant between group differences. One RCT reported improvement in the intervention arm compared with the control arm.</td>
</tr>
<tr>
<td>Combined behavioral/psychoeducational, activity/ rehabilitation, and complementary and alternative medicine interventions vs. usual care</td>
<td>Equivalence</td>
<td>Low</td>
<td>2 RCTs n = 168</td>
<td>Meta-analysis of 2 RCTs showed no statistically significant difference between arms. The SMD was 0.31 (95% CI: -0.01 to 0.63), (I^2) squared = 0.0%, (p = 0.68).</td>
</tr>
</tbody>
</table>

SMD = standardized mean difference; RCT = randomized controlled trial; vs. = versus; NA = not applicable
Blue dot size corresponds to number of participants in the study.
Respiratory Interventions

Description of Included Studies

Eight RCTs (some concerns in at least one risk of bias tool domain) evaluated respiratory interventions for managing dyspnea in patients with advanced cancer,\textsuperscript{19-26} of which five included a crossover design.\textsuperscript{19, 21-24} Table 5 provides an overview of included RCTs.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study characteristics</th>
<th>Intervention description</th>
<th>Followup duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Airflow/ cooling (2 RCTs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wong, 2017\textsuperscript{19}</td>
<td>Single-center, inpatient hospice, N=30, Asia Lung cancer (43%), 97% on supplemental oxygen, baseline $\geq$ 3/10 dyspnea on numeric rating scale No funding</td>
<td>Usual Care: Same nursing care as in intervention arm, supplemental oxygen, rescue medications, posture changes as needed. Airflow/cooling: desk fan to face. Specified 9-inch fan blade, low air speed to start, distance from face per patient preference. After 5 minutes, groups underwent crossover.</td>
<td>5 minutes, then crossover</td>
</tr>
<tr>
<td>Kako, 2018\textsuperscript{20}</td>
<td>Single-center, inpatient palliative care unit, N=40, Asia Lung cancer (38%), other cancers (62%), 50% on supplemental oxygen, baseline $\geq$ 3/10 dyspnea on numeric rating scale, Eastern Cooperative Oncology Group performance status 3-4 Government funding</td>
<td>Placebo: sham control with fan to legs, slowest speed to start. Other settings (distance, location, strength, swing of fan) per patient preference. Airflow/cooling: standing fan to one side of exposed face (region of 2nd to 3rd portion of trigeminal nerve), slowest speed to start. Other settings (distance, location, side of face, strength, swing of fan) per patient preference. Administered by investigator.</td>
<td>5 minutes</td>
</tr>
<tr>
<td><strong>Compressed air and Supplemental oxygen (4 RCTs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booth, 1996\textsuperscript{21}</td>
<td>Multi-center, inpatient hospice unit, N=38, Europe Lung cancer and mesothelioma (58%), other cancers (42%), no prior oxygen use (non-hypoxemic participants) Non-profit funding</td>
<td>Compressed air: room air by nasal cannula at 4L/minute for 15 minutes. Supplemental oxygen: oxygen by nasal cannula at 4L/minute for 15 minutes. After 15 minutes, groups underwent crossover.</td>
<td>15 minutes, then crossover</td>
</tr>
<tr>
<td>Bruera, 1993\textsuperscript{22}</td>
<td>Single center, setting not reported (likely inpatient palliative care unit), N=14, North America Lung cancer and mesothelioma (36%), other cancers (64%), terminal patients, hypoxemic but oxygen needs $&lt; 4L$/minute. No funding source reported</td>
<td>Compressed air: room air by facemask at 5L/minute for 5 minutes. Supplemental oxygen: oxygen by facemask at 5L/minute for 5 minutes. After 5 minutes, groups underwent crossover.</td>
<td>5 minutes, then crossover</td>
</tr>
<tr>
<td>Bruera, 2003\textsuperscript{23}</td>
<td>Single-center, outpatient, N=33, North America Lung cancer and mesothelioma (94%), other cancers (6%),</td>
<td>Compressed air: room air by nasal cannula set at 5L/minute. Delivered for 5 minutes, with patient at rest, followed by 6-minute walk. Supplemental oxygen: oxygen by nasal</td>
<td>11 minutes, then crossover</td>
</tr>
<tr>
<td>Author, year</td>
<td>Study characteristics</td>
<td>Intervention description</td>
<td>Followup duration</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------</td>
<td>--------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Philip, 2006</td>
<td>Multi-center, inpatient and outpatient, N=51, Australia</td>
<td>Lung cancer and mesothelioma (43%), other cancers (57%), ≥ 30/100 on visual analog scale.</td>
<td>15 minutes, then crossover</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-invasive positive pressure ventilation (2 RCTs)</td>
<td></td>
</tr>
<tr>
<td>Hui, 2013</td>
<td>Single-center, inpatient, N=30, North America</td>
<td>Lung cancer and mesothelioma (55%), other cancers (45%), Eastern Cooperative Oncology Group performance status 3-4, ≥ 3/10 dyspnea on numeric rating scale despite supplemental oxygen</td>
<td>2 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Government funding</td>
<td>High Flow Oxygen: Oxygen flow of 10 to 40L/min titrated to comfort. Oxygen was humidified and heated. Administered by a respiratory therapist for 2 hours.</td>
</tr>
<tr>
<td>Nava, 2013</td>
<td>Multi-center, intensive care unit, N=200, Europe and Asia</td>
<td>Lung cancer and mesothelioma (40%), other cancers (60%), life expectancy &lt; 6 months, ≥4/10 on Borg scale</td>
<td>48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No funding</td>
<td>Control: Supplemental oxygen via Venturi mask or reservoir mask (titrated to goal oxygen saturation &gt; 90%).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-invasive positive pressure ventilation (Bi-level Positive Airway Pressure): Level of initial support, inspiratory positive airway pressure of 10 cm and expiratory positive airway pressure of 5 cm of H2O. Increased by a ratio of 2/1, with respiratory rate set at 12/minute.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rescue therapy allowed in both arms: 10 mg of subcutaneous morphine, as needed every 4 hours to reduce dyspnea.</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial

Outcomes

Patient- or Caregiver-reported, or Observational Symptom-related Outcomes
Dyspnea

Eight RCTs assessed the effects of respiratory interventions on dyspnea in patients with advanced cancer.\textsuperscript{20-26}

Two RCTs evaluated airflow/cooling in inpatient hospice or palliative care units.\textsuperscript{19, 20} Both assessed fan to face for 5 minutes, compared with either usual care\textsuperscript{19} or sham intervention (fan to legs).\textsuperscript{20} Both RCTs assessed dyspnea using a 0-10 scale, using a numeric rating scale,\textsuperscript{19} or an Edmonton Symptom Assessment System- Revised.\textsuperscript{20} Both RCTs individually showed statistically significant and clinically meaningful improvement in dyspnea in the intervention arm compared with the control arm.\textsuperscript{19, 20} According to meta-analyses, the calculated standardized mean difference was -1.23 (95\% confidence interval (CI), -1.74 to -0.71; I-squared, 0.0\%; p=0.76) favoring the fan arm, which was both statistically significant and clinically meaningful (Figure 2).\textsuperscript{19, 20} We concluded that fans were effective in improving dyspnea (SOE: Moderate).

Four RCTs evaluated compressed air compared with supplemental oxygen.\textsuperscript{21-24} All RCTs included a crossover design but did not consistently report outcomes after the first and second intervention. Three RCTs assessed dyspnea using the VAS (0-100).\textsuperscript{21, 22, 24} One RCT evaluated non-hypoxemic patients in an inpatient unit reported that both groups had statistically significant improvement in dyspnea (p < 0.001 for both arms), but there was no between group difference (p value not reported).\textsuperscript{21} Effect size was not reported. One RCT evaluated hypoxemic patients (but required less than 4 L/minute of oxygen) found a statistically significant and clinically meaningful improvement in dyspnea scores favoring oxygen, with a mean between group difference of 20.5 (95\% CI, 13.5 to 27.6).\textsuperscript{22} One RCT evaluated inpatients and outpatients found no statistical difference in dyspnea between groups.\textsuperscript{24} The calculated standardized mean difference was -0.23 (95\% CI, -0.79 to 0.31). This RCT also reported categorical data. The percentage of patients with subjective improvement was similar in both groups (calculated RR, 0.80; 95\% CI, 0.29 to 2.20). One RCT assessed dyspnea using a 0-10 numeric rating scale, and evaluated non-hypoxemic patients, found no statistical difference in dyspnea between groups (p=0.52).\textsuperscript{23} Effect size was not reported. We concluded that compressed air and supplemental oxygen did not differ in improving dyspnea (SOE: Low).

Two RCTs evaluated BPAP’s effects on dyspnea in patients with advanced cancer.\textsuperscript{25, 26} One RCT evaluated BPAP versus high flow oxygen (10-40 L/min) in inpatients with baseline dyspnea despite use of supplemental oxygen.\textsuperscript{25} The RCT reported statistically significant decrease in dyspnea on both a numeric rating scale (0-10) and modified Borg scale (0-10) in both arms, but no statistically significant or clinically meaningful between group differences. The calculated standardized mean differences were 0.37 (95\% CI, -0.34 to 1.10) for the numeric rating scale, and -0.18 (95\% CI, -0.90 to 0.53) for the modified Borg scale. The proportion of patients who reported improvement in dyspnea was similar (calculated RR 0.85, 95\% CI, 0.59 to 1.23). We concluded that BPAP and high flow oxygen did not differ in improving dyspnea (SOE: Low).

One RCT evaluated BPAP compared with supplemental oxygen in inpatients with baseline dyspnea found a statistically significant improvement in dyspnea (Borg scale, 0-10) in the BPAP arm, compared with the supplemental oxygen arm (p=0.0012).\textsuperscript{26} The estimated slope difference was -0.58 (95\% CI, -0.92 to -0.23) over the study period of 48 hours. We could not determine if this was clinically meaningful. We concluded that BPAP was effective for improving dyspnea compared to supplemental oxygen (SOE: Low).
Anxiety

One RCT (n=40) evaluated fan to face versus fan to legs reported anxiety using the Edmonton Symptom Assessment System- Revised scale (0-10). The calculated standardized mean difference was -0.11 (95% CI, 0-0.73 to 0.50). We were unable to draw conclusions (SOE: Insufficient).

Functional Status

One RCT (n=33) evaluated compressed air compared with supplemental oxygen reported functional status using a physical function subscale (range, 0-100). The RCT found no statistically significant between group differences (p=0.64). Effect sizes were not reported.

Clinical or Utilization Health Outcomes

Respiratory Rate

Five RCTs reported on the effects of respiratory interventions on respiratory rate in patients with advanced cancer. For airflow/cooling interventions, meta-analysis showed no statistically significant difference in respiratory rate between arms. The calculated standardized mean difference was -0.15 (95% CI, -0.62 to 0.32; I-squared, 0.0%; p=0.69). For BPAP, meta-analysis showed no statistically significant difference in respiratory rate between the BPAP arms and the control arms (high flow oxygen in one RCT, supplemental oxygen in one RCT). The mean between-group difference was -0.754 (95% CI, -1.67 to 0.16; I-squared, 0.0%; p= 0.95). In one RCT, there was a statistically
significant reduction in respiratory rate in the supplemental oxygen arm compared with the compressed air arm. The calculated standardized mean difference was 3.08 (95% CI, 1.46 to 4.70).

**Oxygen or Carbon Dioxide/Bicarbonate Levels (Oxygen Saturation)**

Six RCTs reported on the effects of respiratory interventions on oxygen, carbon dioxide or bicarbonate levels (oxygen saturation) in patients with advanced cancer.\textsuperscript{19, 20, 22, 24-26} One RCT reported improvement in transcutaneous carbon dioxide in the high flow oxygen (10-40 L/min of oxygen) arm compared with the BPAP arm (p=0.02), but no between group differences in oxygen saturation (p=0.62).\textsuperscript{25} Effect sizes were not reported. Another RCT evaluated BPAP compared with oxygen showed a statistically significant difference in the partial pressure of oxygen (PaO2) (mean between group difference 5.17, 95% CI, 1.98 to 8.35) favoring the BPAP arm, but not in the partial pressure of arterial carbon dioxide (PaCO2) (mean between group difference, -1.56; 95% CI, -3.13 to 0.02).\textsuperscript{26}

For supplemental oxygen versus compressed air,\textsuperscript{22, 24} one RCT reported no statistically significant difference in oxygen saturation between arms.\textsuperscript{22} The calculated standardized mean difference was -0.98 (95% CI, -2.10 to 0.13).\textsuperscript{22} Another RCT reported a statistically significant difference in oxygen saturation between groups, favoring the supplemental oxygen arm.\textsuperscript{24} The mean absolute change in oxygen saturation (percentage) from baseline in the supplemental oxygen and compressed air arms was 5.43 percent and 0.94 percent respectively (between group p≤ 0.001).

For airflow/cooling interventions\textsuperscript{19, 20} compared with either usual care or sham intervention (fan to legs), meta-analysis showed no statistically significant difference in oxygen saturation between arms. The calculated standardized mean difference was -0.01 (95% CI, -0.48 to 0.46; I-squared, 0.0%; p=0.647) (Appendix C-Figure 3).

**Heart Rate**

Two BPAP RCTs\textsuperscript{25, 26} and one airflow/cooling RCT reported on the effects on heart rate.\textsuperscript{20} The meta-analysis of the BPAP RCTs showed a statistically significance between group difference in the decrease in heart rate, reduced more in the BPAP arm (mean between-group difference, -2.904; 95% CI, -5.47 to -0.336), (I-squared, 0.0%; p=0.335) (Appendix C-Figure 4).\textsuperscript{25, 26} One RCT evaluated airflow/cooling reported no statistically significant effect on heart rate (calculated standardized mean difference, -0.19; 95% CI, -0.82 to 0.42).\textsuperscript{20}

**Blood Pressure**

Two RCTs evaluated the use of BPAP in patients with advanced cancer reported no statistically significant between group differences in the effects on blood pressure.\textsuperscript{25, 26} The calculated standardized mean differences for systolic blood pressure was -0.62 (95% CI, -1.34 to 0.10) in one RCT\textsuperscript{25}, and the mean between-group difference for blood pressure was -0.51 (95% CI, -21.13 to 1.12) in the other RCT.\textsuperscript{26}

**Objective Measure of Functional Capacity**

One RCT (n=33) evaluated compressed air and supplemental oxygen reported no statistically significant between groups differences in 6-minute walking distance (p=0.95).\textsuperscript{23} Effect sizes were not reported. We were unable to draw conclusions (SOE: insufficient).
Behavioral and Psychoeducational Interventions

Description of Included Studies

Three RCTs (2 with some concerns and 1 with high risk of bias) evaluated behavioral and psychoeducational interventions in patients with advanced cancer. The control arm(s) were usual care in all three RCTs. Table 6 provides an overview of included RCTs.

Table 6. Overview of behavioral and psychoeducational interventions for patients with advanced cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study characteristics</th>
<th>Intervention description</th>
<th>Followup duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bordeleau, 2003&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Multi-center, outpatient, N=215, North America</td>
<td>Usual care: Usual information regarding breast cancer, treatment, relaxation, nutrition</td>
<td>4, 8, 12 months (primary follow up)</td>
</tr>
<tr>
<td></td>
<td>Breast cancer, Eastern Cooperative Oncology Group performance status 0-2, life expectancy &gt;3 months</td>
<td>Other behavioral therapy: Weekly (90 minute) therapist-led supportive-expressive group therapy (foster support and encourage expressing emotions, relaxation exercise at end of session, encouraged to practice at home)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No funding source reported.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McMillan, 2007&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Single-center, home hospice, N=328, North America</td>
<td>Usual care: General hospice care, routine education and support of caregivers as provided in hospice</td>
<td>16 days and 30 days (primary follow up)</td>
</tr>
<tr>
<td></td>
<td>Primary cancer site not reported, Hospice patients with distress and identified caregiver</td>
<td>Friendly visit group: Caregivers received general support without formal COPE (creativity, optimism, planning, and expert information) intervention. Three visits in 9 days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Government funding.</td>
<td>Other behavioral therapy: Problem-based coping intervention (COPE, creativity, optimism, planning, and expert information) on caregivers of patients in home hospice (sessions of 30-45 minutes each, over 9 days).</td>
<td></td>
</tr>
<tr>
<td>Moore, 2012&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Multi-center, outpatient, N=202, Europe</td>
<td>Usual care: Usual care.</td>
<td>3 months (primary follow up), 6 months and 12 months</td>
</tr>
<tr>
<td></td>
<td>Lung cancer and mesothelioma, 85% advanced, World Health Organization performance status 0-2, life expectancy &gt; 3 months</td>
<td>Other behavioral therapy: Multidisciplinary nurse-led follow up (Patients had access to clinical nurse specialists for questions/concerns and could have evaluation for symptoms by phone or in-person). Ensured rapid communication, regular contact and reassurance, coordination of care.</td>
<td></td>
</tr>
</tbody>
</table>

Outcomes

Patient- or Caregiver-reported, or Observational Symptom-related Outcomes
**Dyspnea**

Three RCTs assessed the effects of behavioral or psychoeducational interventions on dyspnea in patients with advanced cancer.\(^{27-29}\) One RCT assessed dyspnea using a dyspnea intensity scale (0-10).\(^{28}\) This RCT evaluated a problem-based coping intervention compared with usual care and an attention control intervention and found no statistically significant between group differences in dyspnea (\(p=0.77\)).\(^{28}\) The random effect model estimate was -0.003 (standard error, 0.011). Two RCTs assessed dyspnea using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).\(^{27,29}\) One RCT evaluated supportive-expressive group therapy compared with usual care found no statistically significant difference between groups. The calculated standardized mean difference was -0.17 (95% CI, -0.30 to 0.26).\(^{27}\)

One RCT evaluated multidisciplinary nurse-led follow up versus usual care reported a statistically significant difference between groups in median dyspnea scores (\(p=0.03\), favoring the intervention arm)\(^{29}\) The RCT only reported a p-value. We could not determine if this was clinically meaningful. Effect sizes were not reported. We concluded that behavioral and psychoeducational interventions did not consistently produce a clinically important improvement in dyspnea (SOE: low).

**Functional Status**

Two RCTs reported on the effects of behavioral or psychoeducational interventions on functional status in patients with advanced cancer, using the EORTC core questionnaire.\(^{27,29}\) One RCT evaluated supportive-expressive group therapy compared with usual care reported no statistically significant difference between groups. The calculated standardized mean difference was -0.21 (95% CI, -0.50 to 0.06).\(^{27}\) One RCT evaluated multidisciplinary nurse-led follow up compared with usual care reported no statistically significant difference between groups (\(p=0.22\)).\(^{29}\) The RCT only reported a p-value. Effect sizes were not reported.

**Health-Related Quality of life**

Three RCTs reported on the effects of behavioral or psychoeducational interventions on health-related quality of life in patients with advanced cancer.\(^{27-29}\)

One RCT reported health-related quality of life using the EORTC QLQ-C30 questionnaire evaluated supportive-expressive group therapy compared with usual care. The study found no statistically significant difference between groups. The calculated standardized mean difference was 0.15 (95% CI, -0.13 to 0.43).\(^{27}\)

One RCT evaluated problem-based coping intervention compared with usual care versus placebo (friendly visit group) found no statistically significant differences in health-related quality of life, using the Hospice Quality-of-Life Index (\(p=0.246\)).\(^{28}\) The random effect model estimate was 0.132 (standard error 0.113).

One RCT evaluated multidisciplinary nurse-led follow up compared with usual care reporting health-related quality of life through the EORTC core questionnaire reported no statistically significant difference between groups (\(p=0.82\)).\(^{29}\) Effect sizes were not reported. We concluded that behavioral and psychoeducational interventions did not improve health-related quality of life (SOE: Low).
Clinical or Utilization Health Outcomes
No RCTs of behavioral and psychoeducational interventions reported any clinical or health care utilization outcomes.

Activity and Rehabilitation Interventions

Description of Included Studies
Four RCTs (1 with some concerns and 3 with high risk of bias) evaluated activity and rehabilitation interventions in patients with advanced cancer, \(^{30-33}\) and one of the four included a crossover design.\(^ {33}\) Two RCTs compared two different interventions, \(^ {32, 33}\) and two RCTs compared interventions with usual care. \(^ {30, 31}\) Table 7 provides an overview of the included RCTs.

Table 7. Overview of activity and rehabilitation interventions for patients with advanced cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study characteristics</th>
<th>Intervention description</th>
<th>Followup duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise therapy (1 RCT)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hwang, 2012(^ {30})</td>
<td>Single-center, outpatient, N=24, Asia Lung cancer with EGFR mutation, age 40-75 years, Eastern Cooperative Oncology Group Performance Status 0-1 Funding source not reported</td>
<td>Usual care: General education, social phone calls, elastic band exercise given if patients asked. Exercise therapy: Trainer-led, high intensity Treadmill/ cycling ergometer, 30-45 minutes sessions thrice weekly x 8 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td><strong>Respiratory training (1 RCT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molassiotis, 2017(^ {31})</td>
<td>Multi-center, outpatient, N=46, Europe Lung cancer/ mesothelioma, 59% advanced cancer, with refractory dyspnea at rest or minimal exertion, life expectancy &gt;3 months Government funding</td>
<td>Usual care: Routine nursing input, opioids, oxygen, use of other medical services, and home visits (same as experimental arm) Respiratory training: Inspiratory muscle training via a pressure threshold device, where participants used the device 5 times a week at home. Coaching in person, monthly home visits to check/coach.</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>Exercise therapy and Respiratory training (2 RCTs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henke, 2014(^ {32})</td>
<td>Single-center, inpatient while receiving chemotherapy, N=29, Europe Lung cancer, Karnofsky Performance Score &gt;50% Funding source not reported</td>
<td>Respiratory training and exercise therapy: Breathing techniques and conventional physiotherapy taught, including massage therapy if needed. Respiratory training and exercise therapy: Combination of exercise training (strength and endurance training, every other day for strength, 5 days a week for endurance) and respiratory training (active cycle of breathing therapy).</td>
<td>9 weeks (approximately)</td>
</tr>
<tr>
<td>Vanderbyl, 2017(^ {33})</td>
<td>Single-center, outpatient, N=24, North America Lung cancer (50%) and gastrointestinal cancers (50%), Eastern Cooperative Qigong therapy: Twice a week therapist-led walking qigong. Follow “in, in, out” breathing pattern. Practice at home for 1 hour daily. Exercise therapy: Twice a week physiotherapist-led supervised exercise (cardiovascular and</td>
<td>6 weeks, then crossover.</td>
<td></td>
</tr>
</tbody>
</table>
Outcomes

Patient- or Caregiver-reported or Observational Symptom-related Outcomes

Dyspnea

Four RCTs assessed the effects of activity and rehabilitation interventions on dyspnea in patients with advanced cancer.30-33

One RCT assessed dyspnea using a Likert scale (0-10) and evaluated exercise compared with Qigong (a mind-body exercise that combines meditation, slow physical movements and controlled breathing) reported no statistically significant difference between groups.33 The calculated standardized mean difference was 0.09 (95% CI, -0.71 to 0.89). The arms then underwent crossover. The study reported no statistically significant difference in dyspnea between groups even after crossover (p=0.61, effect sizes not reported).33

One RCT evaluated inspiratory muscle training compared with usual care31 reported dyspnea using the modified Borg scale (0-10) and found a statistically significant worsening in the usual care arm (p=0.033) and a non-significant change in the inspiratory muscle training arm (p value not reported). The mean difference between groups was 0.80 and did not meet criteria for a clinically meaningful difference.

Two RCTs evaluated dyspnea using the EORTC QLQ-C30 questionnaire.30, 32 One RCT evaluating exercise compared with usual care reported no statistically significant effect on dyspnea (calculated standardized mean difference, -0.35; 95% CI, -1.16 to 0.45).30

One RCT evaluated a combination of exercise/respiratory training compared with conventional therapy 32 reported a statistically significant difference in dyspnea between arms, favoring the combination arm (p <0.05). Effect sizes were not reported.

We could not determine if this was clinically meaningful. We concluded that activity and rehabilitation interventions did not consistently improve dyspnea (SOE: Low).

Anxiety

Two RCTs assessed the effects of activity and rehabilitation interventions on anxiety in patients with advanced cancer. Both RCTs used the Hospital Anxiety and Depression Scale. In one RCT evaluating exercise compared with Qigong, the calculated standardized mean difference was -0.07 (95% CI, -0.87 to 0.73)33 for the first comparison between interventions. The study found no statistically significant difference in dyspnea between groups even after crossover (p=1.00, effect sizes not reported). The order of interventions did not have a statistically significant impact on anxiety (p=0.13).

One RCT evaluated inspiratory muscle training compared with usual care found a statistically significant worsening in mean anxiety scores in the usual care arm, and a non-significant change in the inspiratory muscle training arm (exact p values not given).31 There was
a statistically significant (p=0.027) between-group difference in anxiety, favoring the inspiratory muscle training arm. Effect sizes were not reported. We could not determine if this was clinically meaningful. We were unable to draw conclusions (SOE: Insufficient).

**Functional Status**

Two RCTs evaluated the effects of activity and rehabilitation interventions on functional status through the EORTC QLQ-C30 questionnaire (physical functioning).\(^{30,32}\)

One RCT evaluated exercise compared with usual care reported no statistically significant effect on functional status (calculated standardized mean difference, -0.09; 95% CI, -0.70 to 0.89).\(^{30}\)

One RCT evaluated a combination of exercise and respiratory training compared with conventional therapy\(^ {32}\) reported a statistically significant difference in function between arms, favoring the combination arm (p <0.05). We could not calculate effect sizes or determine if this was clinically meaningful.

**Health-Related Quality of life**

Four RCTs reported on the effects of activity and rehabilitation interventions on health-related quality of life in patients with advanced cancer.\(^{30-33}\) One RCT evaluating exercise compared with Qigong reported no statistically significant effect on health-related quality of life using the Functional Assessment of Cancer Therapy: General (FACT-G) questionnaire (calculated standardized mean difference, 0.008; 95% CI, -0.79 to 0.81)\(^{33}\) for the first comparison between interventions. The trial found no statistically significant difference in dyspnea between groups even after crossover (p=0.70, effect sizes not reported). The order of interventions did have a statistically significant impact; changes in health-related quality of life scores were more favorable during the first intervention period compared with the second (p=0.01).\(^ {33}\)

One RCT evaluated inspiratory muscle training compared with usual care reported health-related quality of life using the Chronic Respiratory Disease Questionnaire.\(^ {31}\) Health-related quality of life scores were better in the inspiratory muscle-training group compared with the usual care group (p value not reported). Effect sizes were not reported. We could not calculate effect sizes or determine if this was clinically meaningful.

Two RCTs reported on health-related quality of life using the EORTC QLQ-C30 questionnaire.\(^ {30,32}\) One RCT evaluating exercise compared with usual care reported no statistically significant effect on health-related quality of life (calculated standardized mean difference, 0.13; 95% CI, -0.67 to 0.93).\(^ {30}\) One RCT evaluated a combination of exercise and respiratory training compared with conventional physiotherapy reported no statistically significant differences in health-related quality of life within or between groups (p > 0.05).\(^ {32}\) We could not calculate effect sizes. We concluded that activity and rehabilitation interventions did not consistently improve health-related quality of life (SOE: Low).

**Clinical or Utilization Health Outcomes**

**Heart Rate**

One RCT (n=24) evaluated exercise compared with usual care in patients with advanced cancer reported no statistically significant effect on heart rate (calculated standardized mean difference, 0.16 ;95% CI, -0.66 to 0.98).\(^ {30}\)
Blood Pressure

One RCT (n=24) evaluated exercise compared with usual care in patients with advanced cancer reported no statistically significant effect on blood pressure (calculated standardized mean difference, 0.42; 95% CI, -0.43 to 1.29).³⁰

Objective Measure of Functional Capacity

Two RCTs assessed the effects of activity and rehabilitation interventions on an objective measure of functional capacity using the 6 minute walking test.³², ³³

In one RCT evaluated exercise compared with Qigong, the calculated standardized mean difference was -1.4 (95% CI, -2.33 to -0.52), favoring the exercise arm.³³ After this first intervention, participants underwent crossover. For patients who completed both sets of interventions, there was also a statistically significant between-group differences in mean meters walked (p=0.02, effect size not reported), favoring the exercise arm.³³ The order of interventions had a statistically significant impact on outcomes; changes in meters walked were more favorable during the first intervention period compared to the second (p 0.008).

One RCT evaluated a combination of exercise and respiratory training compared with conventional physiotherapy³² reported statistically significant differences in mean meters walked in within group and between group comparisons (p < 0.05, for all) favoring the exercise/respiratory training. Effect sizes were not reported. We concluded that activity and rehabilitation interventions improved functional capacity (SOE: Low).

Complementary and Alternative Medicine Interventions

Description of Included Studies

Four RCTs (2 with some concerns and 2 with low risk of bias) evaluated complementary and alternative medicine interventions in patients with advanced cancer. ³⁴-³⁷ Three RCTs evaluated at least one of three types of complementary and alternative medicine interventions: acupuncture, acupressure, or reflexology.³⁴, ³⁶, ³⁷ One RCT evaluated music therapy.³⁵ Table 8 provides an overview of included RCTs.

Table 8. Overview of complementary and alternative medicine interventions for patients with advanced cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study characteristics</th>
<th>Intervention description</th>
<th>Followup duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acupressure (1 RCT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dogan, 2019³⁷</td>
<td>Single-center, outpatient, N=60, Asia Lung cancer, 97% advanced, life expectancy &gt;3 months, ≥ 3/10 dyspnea on modified Borg scale Funding source not reported.</td>
<td>Usual care: received usual care Acupressure: First session with investigator in person. Daily acupressure at home (36 minutes daily). Three selected sites (LU-1, LU-10, P-6) marked by surgical pen and training guide/ tool given to patients and primary care providers. Weekly check ins by phone.</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Acupuncture and acupressure (1 RCT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vickers, ³⁴</td>
<td>Single-center, inpatient and outpatient, N=45, North America</td>
<td>Placebo: Sham acupuncture needles (blunted needles) applied in body areas away from breathlessness sites, for 15 minutes, by Licensed acupuncturists. Then, sham acupressure studs</td>
<td>15 minutes, and 1 week</td>
</tr>
</tbody>
</table>
### Study characteristics

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study characteristics</th>
<th>Intervention description</th>
<th>Followup duration</th>
</tr>
</thead>
</table>
| Lung (80%) or breast (20%) cancer, American Thoracic Society Breathlessness score 2 or higher  
Government funding. | inserted 1 hour after removal of acupuncture needles—patients rub approx. 3x/ day at home x 1 week.  
Acupuncture/ acupressure: True acupuncture needles applied to depth of 0.5-1.5 cm (including auricular points) at breathlessness sites, elicit de qi, no movement after placing needles, for 15 minutes, by licensed acupuncturists. Then, stainless steel acupressure studs applied, patients rub approximately 3x/ day at home x 1 week. | | 

**Reflexology (1 RCT)**

| Wyatt, 2012 | Multi-center, outpatient, N=286, North America  
Breast cancer, able to perform basic activities of daily living.  
Government funding. | Usual care: received usual care  
Lay foot manipulation: Superficially similar to reflexology but avoided the 9 zones and deep thumb pressure, provided weekly for 4 weeks, each session was 30 minutes, administered by lay women.  
Reflexology group: Stimulation of 9 essential breast cancer specific reflexes using deep thumb walking pressure, provided weekly for 4 weeks, each session was 30 minutes, administered by certified reflexologists. | 5 weeks and 11 weeks (primary follow up) |

**Music Therapy (1 RCT)**

| Ramirez, 2018 | Single-center, inpatient palliative care unit, N=40, Europe  
Primary cancer site not reported, terminally ill patients.  
Government and non-profit funding. | Placebo: Music therapist provides company and discusses music and preferences but without playing music for 30 minutes.  
Music therapy: Participants interviewed about music preferences, and instrumental/vocal music played by music therapist for 30 minutes. | 30 minutes |

RCT = randomized controlled trial

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### Outcomes

**Patient- or Caregiver-reported or Observational Symptom-related Outcomes**

**Dyspnea**

Four RCTs assessed the effects of complementary and alternative medicine interventions on dyspnea in patients with advanced cancer.34-36

One RCT used the “additional concerns” scale of the Functional Assessment of Cancer Therapy–Breast (FACT-B), version 4 questionnaire (scale, 0 to 4) and reported statistically significant improvement in dyspnea with reflexology.36 The calculated standardized mean difference for reflexology compared with control was 0.36 (95% CI, 0.07 to 0.64). This was not clinically meaningful when extrapolated to a 0-10 scale. The calculated standardized mean difference for lay foot manipulation compared with control was 0.23 (95% CI, -0.04 to 0.52).
One RCT evaluated acupuncture and acupressure reported no statistically significant difference in dyspnea (using a 0-10 dyspnea scale) between groups. The calculated standardized mean difference was 0.10 (95% CI, -0.59 to 0.79) at 15 minutes and 0.35 (95% CI, -0.63 to 1.32) at 7 days.34

One RCT assessed dyspnea using the modified Borg scale (0-10) evaluating acupressure reported a statistically significant between group difference in median dyspnea scores, both before a 6 minute walking test (p=0.004) and after a 6 minute walking test (p=0.018) favoring the acupressure arm.37 We could not determine if this was clinically meaningful. We concluded that acupuncture/acupressure/reflexology were more effective at reducing dyspnea than usual care or sham procedures (SOE: Low).

One RCT evaluated music therapy reported statistically significant improvement in dyspnea scores (Edmonton Symptom Assessment System, 0-10) in the music therapy group (p=0.042) but not in the placebo group. Between group differences and effect sizes were not reported.35 We could not determine if this was clinically meaningful. We could not draw a conclusion about music therapy (SOE: Insufficient).

Anxiety
Two RCTs assessed the effects of complementary and alternative medicine on anxiety in advanced cancer patients.35, 36

One RCT reported the State-Trait Anxiety Inventory for anxiety.36 The trial found no statistically significant difference in anxiety between the reflexology versus control arms (beta estimate, -0.886; standard error of beta, 1.259; p=0.48), and lay foot manipulation versus control arms (beta estimate, 1.622; standard error of beta, 1.255; p=0.2). We could not draw a conclusion about reflexology (SOE: Insufficient).

One RCT reported statistically significant improvement in anxiety scores (ESAS, 0-10) in the music therapy group (p=0.002) but not in the placebo group. Between group differences and effect sizes were not reported.35 We could not determine if this was clinically meaningful. We could not draw a conclusion about music therapy (SOE: insufficient).

Functional Status
One RCT (n=286) reported on the effects of reflexology on functional status using the physical function subscale of the 36-Item Short Form Survey (range, 0-100).36 The mean improvement in physical functioning for the reflexology group compared to the control group was statistically significant (p=0.04). The adjusted effect sizes for reflexology versus control were estimated to be 0.21 at week 5 and 0.44 at week 11. We could not determine if this was clinically meaningful.

Health-Related Quality of life
Two RCTs reported on the effects of complementary and alternative medicine on health-related quality of life in patients with advanced cancer.36, 37

One RCT reported health-related quality of life using the St George’s Respiratory Questionnaire (0-100), 37 and the other reported health-related quality of life using the Functional Assessment of Cancer Therapy–Breast (FACT-B), version 4 questionnaire (0-180).36 Meta-analysis of these two RCTs showed a statistically significant difference in health-related quality of life between arms, favoring the intervention arm. The meta-analysis should be interpreted with caution given the substantial heterogeneity. The calculated standardized mean
difference was -0.565 (95% CI, -0.87 to -0.26), (I-squared = 98.5%, p=0.000) (Appendix C-Figure 6). We concluded that acupuncture/acupressure/reflexology were more effective at improving health-related quality of life than usual care (SOE: Low).

Clinical or Utilization Health Outcomes

One RCT (n=60) reported on respiratory rate, heart rate, oxygen saturation (both before and after a 6 minute walking test) and 6 minute walking distances, with acupressure and usual care.37 Acupressure significantly improved respiratory rate (p≤ 0.001) and 6 minute walking distances (p=0.046) but not oxygen saturation or heart rate, compared to usual care. We could not calculate effect sizes. We were unable to draw conclusions about functional capacity (SOE: Insufficient).

Multicomponent Interventions

Combined Activity/Rehabilitation and Behavioral/Psychoeducational Interventions

Description of Included Studies

Two RCTs with high risk of bias evaluated a combination of activity/rehabilitation and behavioral/psychoeducational interventions in patients with advanced cancer.38, 39 Table 9 provides an overview of included RCTs.

Table 9. Overview of activity and rehabilitation and behavioral psychoeducational interventions for patients with advanced cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study characteristics</th>
<th>Intervention description</th>
<th>Followup duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corner, 199638</td>
<td>Single-center, outpatient, N=20, Europe Lung cancer Non-profit funding</td>
<td>Control: Usual care (Allowed to talk freely about dyspnea but no specific counseling/retraining) Intervention: Respiratory training (breathing re-training) and behavioral therapy (counselling, relaxation, coping) sessions, once weekly in a nurse-led clinic.</td>
<td>4 weeks and 12 weeks (primary follow up).</td>
</tr>
<tr>
<td>Chan, 201139</td>
<td>Single-center, outpatient, N=140, Asia Lung cancer, Karnofsky Performance Scale &gt;60%, receiving palliative radiation. Government funding.</td>
<td>Control: Usual care Intervention: Respiratory training (new breathing technique, positioning, relaxation exercises) and behavioral therapy (education package and in-person coaching on relaxation, coping, and self-care), done at baseline and at 3 weeks.</td>
<td>3, 6 and 12 weeks (primary follow up).</td>
</tr>
</tbody>
</table>

Outcomes

Patient- or Caregiver-reported or Observational Symptom-related Outcomes
Dyspnea

Two RCTs assessed dyspnea using the VAS (0-10).\textsuperscript{38, 39} One RCT reported within group median improvements in dyspnea scores of -0.5 (range, -5.7 to 1) in usual care, and 0.5 (range, -0.5 to 2.8) in intervention arms.\textsuperscript{38} The median between group differences was statistically significant (p<0.02), favoring the intervention arm. Effect sizes were not reported. We could not determine if this was clinically meaningful.

One RCT reported statistically significant between group differences in mean dyspnea at 6 weeks (p=0.002, partial eta-squared 0.04) and 12 weeks (p=0.001, partial eta-squared 0.043).\textsuperscript{39} These indicate small effect sizes. We could not determine if this was clinically meaningful. We concluded that combination activity and rehabilitation, and behavioral psychoeducational interventions were more effective at reducing dyspnea compared with usual care (SOE: Low).

Anxiety

Two RCTs assessed anxiety.\textsuperscript{38, 39} One RCT reported anxiety using the Hospital Anxiety and Depression Scale, and reported within group median improvements in anxiety scores of 0 (range, -1 to 3) in usual care, and 1.5 (range, 0-5) in intervention arms.\textsuperscript{38} The between group differences in median anxiety were statistically non-significant (exact p value not reported). Effect sizes were not reported.

Another RCT reported anxiety using the State-Trait Anxiety Inventory and found statistically significant between group differences in mean anxiety scores at 6 weeks (p=0.001, partial eta-squared 0.051) and 12 weeks (p=0.005, partial eta-squared 0.035).\textsuperscript{39} These indicate small effect sizes. We could not determine if this was clinically meaningful. We concluded that a combination of activity and rehabilitation, and behavioral psychoeducational interventions were more effective at improving anxiety compared with usual care (SOE: Low).

Functional Status

Two RCTs assessed functional status.\textsuperscript{38, 39} One RCT reported the difficulties in performing activities of daily living (as reported on the Functional Capacity Scale), and reported within group median improvements in functional status scores of 0 (range, -3 to 2) in usual care, and 3 (range, -3 to 8) in intervention arms.\textsuperscript{38} The between group differences in median functional status were statistically significant (p < 0.03). We could not determine if this was clinically meaningful. Effect sizes were not reported.

Another RCT reported the 36-Item Short Form Survey and found statistically significant between group differences in mean functional status scores at 6 weeks (p=0.000, effect sizes not reported) and 12 weeks (p=0.002, effect sizes not reported).\textsuperscript{39} We could not determine if this was clinically meaningful.

Clinical or Utilization Health Outcomes

No RCTs of a combination of activity and rehabilitation and behavioral and psychoeducational interventions reported any clinical or utilization health outcomes.
Combined Activity/Rehabilitation, Behavioral/Psychoeducational, and Complementary and Alternative Medicine Interventions

Description of Included Studies

Two RCTs with high risk of bias evaluated a combination of activity/rehabilitation, behavioral/psychoeducational, and complementary and alternative medicine interventions.\textsuperscript{40, 41} One of them had a crossover design (i.e., delayed intervention), where the control group received the intervention after 2 weeks.\textsuperscript{41} However, no outcomes after crossover were presented. Table 10 provides an overview of included RCTs.

Table 10. Overview of activity/rehabilitation, behavioral/psychoeducational, and complementary and alternative medicine interventions for patients with advanced cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study characteristics</th>
<th>Intervention description</th>
<th>Followup duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yorke, 2015\textsuperscript{40}</td>
<td>Multi-center, primarily outpatient, N=101, Europe Lung cancer, 59% advanced, World Health Organization Performance Status 0-2 Non-profit funding</td>
<td>Control: usual care Intervention: Respiratory training (breathing re-training and cough easing techniques), behavioral therapy (counselling, caregiver support, acceptance, locus control), and acupressure.</td>
<td>4 weeks and 12 weeks (primary followup).</td>
</tr>
<tr>
<td>Farquhar, 41</td>
<td>Single-center, outpatient, N=67, Europe Lung cancer/ mesothelioma (54%), referred to breathlessness service Government and non-profit funding</td>
<td>Control: usual care Intervention: Home visits and telephone calls by multidisciplinary staff to encourage respiratory training, behavioral training, and mindfulness. Control group received intervention after 2 weeks.</td>
<td>2 weeks; data for crossover not presented separately.</td>
</tr>
</tbody>
</table>

Outcomes

Patient- or Caregiver-reported, or Observational Symptom-related Outcomes

Dyspnea

Two RCTs assessed dyspnea using the Numeric Rating Scale (0 to 10).\textsuperscript{40, 41} In one RCT, the mean between group difference was not statistically significant, 0.65 (95% CI, -0.49 to 1.80)\textsuperscript{40}. This RCT also reported the Dyspnea-12 scale (range, 0 to 36).\textsuperscript{40} The mean between group difference was 5.19 (95% CI, 0.62 to 9.75) and was statistically significant (p=0.026) favoring the intervention arm.

In the other RCT, the mean between group difference was -1.29 (95% CI, -2.57 to -0.005) and was statistically significant (p=0.049) and clinically meaningful, favoring the intervention arm.\textsuperscript{41} We concluded that multicomponent activity and rehabilitation, behavioral psychoeducational, and complementary and alternative medicine interventions were more
effective at improving dyspnea than usual care (SOE: Low).

**Anxiety**

Two RCTs assessed anxiety using the Hospital Anxiety and Depression Scale\(^{40,41}\). Meta-analysis demonstrated no statistically significant difference between arms. The calculated standardized mean difference was 0.20 (95% CI, -0.12 to 0.52), (I-squared = 0.0%; p = 0.42) (Appendix C-Figure 5). We concluded that multicomponent activity and rehabilitation, behavioral psychoeducational, and complementary and alternate medicine interventions were not effective at improving anxiety compared to usual care (SOE: low).

**Health-Related Quality of life**

Two RCTs assessed health-related quality of life using the 3-level version of the EuroQol-5D (EQ-5D-3L) score at 12 weeks\(^{40}\) and Chronic Respiratory Questionnaire (CRQ)-7 at 2 weeks\(^{41}\). Meta-analysis demonstrated no statistically significant difference between arms. The calculated standardized mean difference was 0.31 (95% CI, -0.01 to 0.63), (I-squared = 0.0%, p = 0.68). We concluded that multicomponent activity and rehabilitation, behavioral psychoeducational, and complementary and alternative medicine interventions were not effective at improving health-related quality of life compared with usual care (SOE: Low).

**Clinical or Utilization Health Outcomes**

**Hospitalizations**

One RCT (n=67) reported hospitalizations over a 2-week period. The calculated RR for hospitalization was 0.62 (95% CI: 0.11 to 3.41), in the intervention arm relative to the control arm\(^{41}\).

**Behavioral and Psychoeducational and Complementary or Alternative Medicine Interventions**

**Description of Included Studies**

One single-center RCT with some concerns in at least one risk of bias tool domain enrolled 50 outpatients with lung cancer whose caregivers reported at least subclinical distress\(^{42}\). Participants and caregivers were randomized to receive either weekly telephone-based acceptance and commitment therapy (including mindfulness), or an intervention with general education and support. Funding was via a non-profit organization. The RCT assessed outcomes using the Memorial Symptom Assessment Scale for dyspnea and Patient-Reported Outcomes Measurement Information System for anxiety at 2 and 6 weeks.

**Outcomes**

**Patient- or Caregiver-reported, or Observational Symptom-related Outcomes**

**Dyspnea**
One RCT (n=50) reported no statistically significant effect on dyspnea (calculated standardized mean difference, 0.46; 95% CI, -0.10 to 1.02). We could not draw a conclusion (SOE: insufficient).

**Anxiety**

One RCT (n=50) reported no statistically significant effect on anxiety (calculated standardized mean difference, 0.11; 95% CI, -0.54 to 0.57). We could not draw a conclusion (SOE: insufficient).

**Clinical or Utilization Health Outcomes**

No RCTs of behavioral and psychoeducational and complementary or alternative medicine interventions reported any clinical or utilization health outcomes.
KQ2. What are the comparative benefits of pharmacological interventions (either alone or in combination) for improving dyspnea in patients with advanced cancer?

Key Points

- Opioids were not more effective than placebo for improving dyspnea in patients with advanced cancer for the types of dyspnea evaluated (short-term exertional or incident dyspnea) (SOE: Moderate). In addition, there was no difference between doses or routes of opioids (SOE: Low).
- Anxiolytics were not more effective than placebo for improving dyspnea or anxiety in patients with advanced cancer (SOE: Low).
- Opioids were not more effective than anxiolytics for improving dyspnea in patients with advanced cancer (SOE: Low).
- We were unable to draw conclusions for corticosteroids or comparisons between other pharmacological interventions for improving dyspnea or anxiety in patients with advanced cancer (SOE: Insufficient).
- Opioids were not more effective than placebo for improving functional capacity in patients with advanced cancer as measured by a six-minute walk test (SOE: Moderate).
- We were unable to draw conclusions about the effects of pharmacological interventions for improving health-related quality of life in patients with advanced cancer (SOE: Insufficient).

Table 11. Summary of key results for the effects of pharmacological interventions on dyspnea in patients with advanced cancer

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Evidence of difference</th>
<th>Strength of evidence</th>
<th>Total population size (n) and study number</th>
<th>Key findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled comparisons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Opioids vs. placebo | Equivalence | Moderate | 5 RCTs n = 97 | Pooled analysis with Charles, 2008:  
| | | | Fentanyl vs. placebo (4)  
<p>| | | | Hydromorphone (nebulized) vs. hydromorphone (Oral or subcutaneous) vs. placebo (nebulized) (1) | Opioids are not more effective than placebo for improving exertional or incident |</p>
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Evidence of difference</th>
<th>Strength of evidence</th>
<th>Total population size (n) and study number</th>
<th>Key findings</th>
<th>conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytics vs. placebo</td>
<td>Equivalence</td>
<td>Low</td>
<td>2 RCTs n = 452</td>
<td>Buspirone vs. Placebo: • Reported MBGD: -0.52; 95% CI: -1.045 to 0.005</td>
<td>Anxiolytics are no more effective than placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Midazolam vs. Placebo: • No statistically significant difference between groups (p=0.75) at 60 minutes. • Unable to calculate SMD, data presented as number of spray bottles rather than number of participants.</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids vs. placebo</td>
<td>No conclusion drawn</td>
<td>Insufficient</td>
<td>1 RCT n = 41</td>
<td>Calculated SMD: -0.06; 95% CI: -0.7 to 0.58</td>
<td>NA</td>
</tr>
<tr>
<td>Drug-drug comparisons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid vs. opioid</td>
<td>Equivalence</td>
<td>Low</td>
<td>5 RCTs n = 120</td>
<td>Pooled analysis: • SMD: 0.09 (95% CI: -0.32 to 0.5) • I-squared=25%, p=0.26</td>
<td>There was no difference between opioid doses or routes in treating dyspnea</td>
</tr>
</tbody>
</table>

- **SMD** (Standardized Mean Difference)
- **CI** (Confidence Interval)
- **MBGD** (Mean Change from Baseline)
- **I-squared** (Heterogeneity Index)
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Evidence of difference</th>
<th>Strength of evidence</th>
<th>Total population size (n) and study number</th>
<th>Key findings</th>
<th>conclusion</th>
</tr>
</thead>
</table>
| Opioids vs. anxiolytics        | Equivalent              | Low                  | 2 RCTs n = 164                             | For dyspnea intensity:  
  • One study found midazolam was more effective than morphine at 5 days (p<0.001)  
  • Second study found no significant differences between groups at 24 h or 48 h  
For categorical variable of percent not experiencing dyspnea relief:  
  • Calculated RR: 0.075; 95% CI, 0.004 to 1.27  
  • Calculated RR: 1.33; 95% CI, 1.02 to 1.75 | Opioids are not more effective than anxiolytics for improving dyspnea |

| Opioid vs. corticosteroids vs. bronchodilators | No conclusion drawn | Insufficient | 1 retrospective cohort n = 343 | Methylprednisolone vs. aminophylline:  
  • Calculated SMD, 0.41; 95% CI, 0.15 to 0.68  
Morphine vs. aminophylline,  
  • Calculated SMD, 1.18; 95% CI, 0.9 to 1.46  
Morphine vs. methylprednisolone,  
  • Calculated SMD, 0.76; 95% CI: 0.49 to 1.03 | NA |

SMD: standardized mean difference; RR: relative risk; MBGD: mean between group difference; vs= versus; NA=not applicable  
the diameter of each blue circle is linearly related to the number of patients in trials of that comparison/outcome
Table 12. Summary of key results for the effects of pharmacological interventions on anxiety, health-related quality of life, and functional capacity in patients with advanced cancer

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Evidence of difference</th>
<th>Strength of evidence</th>
<th>Total population size (n) and study number</th>
<th>Key findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled comparisons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiolytics vs. Placebo</td>
<td>Equivalence</td>
<td>Low</td>
<td>2 RCTs n = 379</td>
<td>Buspirone vs. placebo</td>
<td>Anxiolytics are no more effective than placebo in treating anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No statistically significant differences between groups; unable to</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>calculate SMD.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intranasal midazolam vs. placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No difference between arms reported by authors</td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids vs. Placebo</td>
<td>No conclusion drawn</td>
<td>Insufficient</td>
<td>1 RCT n = 38 oral dexamethasone vs. placebo</td>
<td>Calculated SMD, -0.06; 95% CI, -0.7 to 0.58</td>
<td>NA</td>
</tr>
<tr>
<td>Functional capacity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid vs. placebo</td>
<td>Equivalence</td>
<td>Moderate</td>
<td>3 RCTs n = 57</td>
<td>Pooled analysis of 2 studies:</td>
<td>Opioids are not more effective than placebo for improving functional</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• SMD, 0.13; 95% CI, -0.46 to 0.72</td>
<td>capacity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• I-squared=0.0%; p=0.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Third study reported no significant differences between groups. Unable to</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>calculate SMD, data reported as medium, rather than mean average.</td>
<td></td>
</tr>
</tbody>
</table>

SMD: standardized mean difference; RR: relative risk; MBGD: mean between group difference; vs= versus; NA=not applicable. The diameter of each blue circle is linearly related to the number of patients in trials of that comparison/outcome.
Description of Included Studies

We identified 15 studies (14 RCTs and 1 retrospective study) including 1,192 patients assessing the benefits of medications for the management of dyspnea in advanced cancer.43-57 Fifteen studies assessed eight different medications over eight different routes of administration. Eight RCTs were placebo-controlled, and six RCTs and one retrospective study assessed comparisons between drugs. Six RCTs evaluated treatments for exertional dyspnea while five evaluated dyspnea at rest. Two RCTs and one retrospective study did not report the type of dyspnea evaluated and one reported on incident dyspnea. Follow-up ranged from 6 minutes to 28 days. Four RCTs were multicenter.45, 53, 54, 57 Three RCTs were industry-funded, all of which assessed fentanyl in various routes of administration (buccal, intranasal, and sublingual).44, 46, 56 Six RCTs and one retrospective study were supported by government funding44-47, 54-56 and 10 RCTs were supported by non-profit organizations.43, 44, 46-48, 50-52, 56, 57 One RCT did not report a funding source53 and one reported no funding.49

The characteristics of the studies, participants, and interventions are listed in Appendix D-Evidence Tables 2, 5, 9, 10 and 14. See Appendix D Evidence Tables 41 through 50 for details of the outcome data. The summary of key findings and strength of evidence are presented in Tables 11 and 12.

Wherever it says “calculated” in the results, those are the calculations done by us.

Outcomes

Patient- or Caregiver-reported, or Observational Symptom-related Outcomes

Dyspnea

Placebo-Controlled Comparisons

Opioids Versus Placebo

Five RCTs (1 with some concerns, 3 with low, and 1 with high risk of bias) assessed the effect of opioids compared with placebo on dyspnea.43, 44, 46, 48, 49 Four RCTs compared fentanyl products (intranasal, buccal, transmucosal and subcutaneous) for the treatment of exertional dyspnea.44, 46, 48, 49 One RCT evaluated hydromorphone (nebulized or subcutaneous) compared with nebulized saline in incident dyspnea.43 Based on the overall pooled results from the meta-analysis, opioids were not more effective than placebo for improving exertional or incident dyspnea in advanced cancer patients after 6 to 10 minutes (SOE: Moderate). Two meta-analyses are reported here to reflect the two placebo comparisons provided in one of the RCTs43 (calculated standardized mean difference with Charles, 2008 et al.43 saline versus nebulized hydromorphone comparison, -0.03; 95% CI, -0.39 to 0.32, I-squared=0.0%) (calculated standardized mean difference with Charles, 2008 et al.43 saline versus systemic hydromorphone comparison, -0.06; 95% CI, -0.41 to 0.3, I-squared=0.0%)(Figures 3 and 4).
Figure 3. Meta-analysis of the effects on dyspnea in randomized controlled trials comparing opioids with placebo in patients with advanced cancer (including Charles, 2008\textsuperscript{43} saline versus nebulized hydromorphone comparison).

<table>
<thead>
<tr>
<th>Author, year Tool Followup</th>
<th>Study size</th>
<th>Favors intervention</th>
<th>Favors control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles, 2008 VAS 10 minutes</td>
<td>40</td>
<td>0.18 (0.44, 0.80)</td>
<td></td>
</tr>
<tr>
<td>Hui, 2014 NRS Second Walk test, not specified time</td>
<td>20</td>
<td>0.09 (-0.79, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Hui, 2016 NRS Second Walk, 20 minutes</td>
<td>24</td>
<td>-0.21 (-1.01, 0.59)</td>
<td></td>
</tr>
<tr>
<td>Hui, 2017 NRS Second Walk test, not specified time</td>
<td>20</td>
<td>-0.67 (-1.58, 0.24)</td>
<td></td>
</tr>
<tr>
<td>Pinna, 2015 NRS 60 minutes</td>
<td>22</td>
<td>0.20 (-0.63, 1.04)</td>
<td></td>
</tr>
<tr>
<td>Overall (I\textsuperscript{-} squared = 0.0%, p = 0.574)</td>
<td></td>
<td>-0.03 (-0.38, 0.32)</td>
<td></td>
</tr>
</tbody>
</table>

VAS=visual analog scale; NRS= numerical rating scale; SMD =standardized mean difference
Blue dot size=corresponds to study size.
Length of the bar=corresponds to range of confidence interval.
Blue diamond=the result when all of the individual studies are combined together and averaged.
Figure 4. Meta-analysis of the effects on dyspnea in randomized controlled trials comparing opioids with placebo in patients with advanced cancer (including Charles, 2008\(^43\) saline versus systemic hydromorphone comparison)

<table>
<thead>
<tr>
<th>Author, year Tool Followup</th>
<th>Study size</th>
<th>Favors intervention</th>
<th>Favors control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles, 2008 VAS 10 minutes</td>
<td>40</td>
<td>0.11 (-0.51, 0.73)</td>
<td></td>
</tr>
<tr>
<td>Hui, 2014 NRS Second Walk test, not specified time</td>
<td>20</td>
<td>0.09 (-0.79, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Hui, 2016 NRS Second Walk, 20 minutes</td>
<td>24</td>
<td>-0.21 (-1.01, 0.59)</td>
<td></td>
</tr>
<tr>
<td>Hui, 2017 NRS Second Walk test, not specified time</td>
<td>20</td>
<td>-0.67 (-1.58, 0.24)</td>
<td></td>
</tr>
<tr>
<td>Pinna, 2015 NRS 60 minutes</td>
<td>22</td>
<td>0.20 (-0.63, 1.04)</td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.621)</td>
<td></td>
<td>-0.06 (-0.41, 0.30)</td>
<td></td>
</tr>
</tbody>
</table>

VAS=visual analog scale; NRS= numerical rating scale; SMD =standardized mean difference

Blue dot size=corresponds to study size.
Length of the bar=corresponds to range of confidence interval.
Blue diamond=the result when all of the individual studies are combined together and averaged.

Anxiolytics Versus Placebo
Two RCTs (1 with some concerns and 1 with low risk of bias) assessed the effect of anxiolytics compared with placebo on dyspnea in patients with advanced cancer.\(^45\), \(^57\)

One RCT compared oral buspirone with placebo to treat exertional dyspnea. Dyspnea was assessed after 28 days using the Oxygen Cost Diagram, a VAS scale assessing tolerance for exertion with scores ranging from 2 to 14.\(^45\) The study found no statistically significant difference between groups (reported mean between-group difference, -0.52; 95% CI, -1.045 to 0.005).

Another RCT evaluated intranasal midazolam versus placebo over 60 minutes and found no statistically significant difference in dyspnea between groups (p=0.75).\(^57\) We were unable to calculate a standardized mean difference, as data were presented based on number of spray bottles of midazolam or placebo used, rather than number of participants.

Based on the available evidence, anxiolytics were not more effective than placebo for the treatment of dyspnea (SOE: Low).

Corticosteroids Versus Placebo
One RCT with low risk of bias compared oral dexamethasone with placebo and assessed
dyspnea at 7 days in patients with advanced cancer. This RCT reported no statistically significant effect for corticosteroids compared with placebo in dyspnea (calculated standardized mean difference, -0.06; 95% CI, -0.7 to 0.58). We were unable to draw conclusions for the effectiveness of corticosteroids compared to placebo for the treatment of dyspnea in advanced cancer (SOE: Insufficient).

Drug-Drug Comparisons

Opioids Versus Opioids

Five RCTs (1 with some concerns, 3 with high, and 1 with low risk of bias), compared the effect of either different routes of administration or different doses of opioids for the treatment of dyspnea in patients with advanced cancer. Two RCTs compared different routes of morphine administration (subcutaneous versus sublingual morphine, and subcutaneous versus nebulized morphine) while a third RCT compared different routes of hydromorphone administration (nebulized versus systemic). Two other RCTs compared different doses of opioid (high dose versus low dose fentanyl, and low dose versus high dose opioids). For the fentanyl RCT, the dose was calculated as either 35 percent to 45 percent of the total opioid dose (high dose group) compared with 15 percent to 25 percent of the patient’s total opioid dose (low dose group) to treat exertional dyspnea. The other RCT did not specify which opioids were used – the groups were divided as 25 percent of the current four-hour total of opioid (low dose) compared with 50 percent (high dose). Based on the results of the meta-analysis of three RCTs, no difference was seen between opioid doses or routes in treating dyspnea in advanced cancer patients (calculated standardized mean difference, 0.09; 95% CI, -0.32 to 0.5, I-squared=25%) (Figure 5) (SOE: Low).

Two RCTs could not be included in the analysis as they reported results as median, rather than mean or data were derived from figures. One RCT evaluated subcutaneous versus nebulized morphine and reported no statistically significant differences between groups at 60 minutes. The other RCT evaluated high dose versus low dose opioids and reported no significant differences between groups.
Figure 5. Meta-analysis of the effects on dyspnea in randomized controlled trials comparing opioids with opioids in patients with advanced cancer

<table>
<thead>
<tr>
<th>Author, year Tool Followup</th>
<th>Study size</th>
<th>Favors intervention</th>
<th>Favors control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles, 2008 VAS 10 minutes</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamborg, 2013 VAS 1 hour</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hui, 2019 Borg Second walk, not specified</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 25.0%, p = 0.263)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| VAS=visual analog scale; SMD =standardized mean difference  
Blue dot size=corresponds to study size.  
Length of the bar=corresponds to range of confidence interval.  
Blue diamond=the result when all of the individual studies are combined together and averaged.  

Opioids Versus Anxiolytics

Two RCTs (1 with some concerns and 1 with high risk of bias) evaluated the effect of midazolam compared with morphine or the combination of both drugs in patients with advanced cancer. In one RCT of oral morphine compared with oral midazolam, midazolam was more effective at relieving dyspnea at 5 days (p<0.001). We were unable to calculate a standardized mean difference, as data could only be abstracted from figures. The study reported no statistically significant differences in the percent of patients with a “therapeutic failure,” defined as a dyspnea intensity on the numeric rating scale greater than 8 at 5 days, between groups (calculated RR, 0.075; 95% CI, 0.004 to 1.27).

Another RCT compared subcutaneous morphine with subcutaneous midazolam or both. The study found no statistically significant differences in dyspnea intensity at 24 or 48 hours. We were unable to calculate a standardized mean difference as data were reported as medians, rather than means. The combination morphine and midazolam group, however, did have a statistically significantly higher percentage of patients reporting dyspnea relief than either agent alone at 24 hours, which was persistent compared with the midazolam-alone group at 48 hours. The study also found that there was a statistically significant difference between groups in the percent of patients with no dyspnea relief at 24 hours, favoring the combination group (calculated RR, 1.33; 95% CI, 1.02 to 1.75).

Given the clinically meaningful differences in patient populations (ambulatory patients with advanced cancer and patients with terminal advanced cancer, life expectancy less than 1 week), we did not conduct a meta-analysis. We concluded that opioids were not more effective than anxiolytics for improving dyspnea (SOE: Low).
Opioids Versus Corticosteroids Versus Bronchodilators

One single-center retrospective cohort study with serious risk of bias evaluated morphine compared with methylprednisolone or aminophylline.55 Patients received morphine, either 5 mg subcutaneously (SC) or 10 percent of their total opioid dose, if opioid tolerant, compared with 40 mg of intravenous (IV) methylprednisolone or 0.25 g of IV aminophylline. At 60 minutes, there was a statistically significant difference (p=0.000) between groups in dyspnea intensity. Specifically, methylprednisolone was more effective than aminophylline (calculated standardized mean difference, 0.41; 95% CI, 0.15 to 0.68) and morphine was more effective than either of the other agents (morphine versus aminophylline, calculated standardized mean difference, 1.18; 95% CI, 0.9 to 1.46) (morphine versus methylprednisolone, calculated standardized mean difference, 0.76; 95% CI: 0.49 to 1.03). The study reported a statistically significant difference in effective rate [reducing the VAS score by at least 50%], with morphine providing a more significant rate of dyspnea relief (p<0.01). We were unable to draw conclusions for the comparative effectiveness of these three interventions because of the high risk of study limitations and imprecise results (SOE: Insufficient).

Anxiety

Placebo-Controlled Comparisons

Anxiolytics Versus Placebo

Two RCTs (1 with some concerns and 1 with low risk) compared the use of anxiolytics with placebo for the treatment of anxiety in advanced cancer patients. One RCT of buspirone versus placebo assessed anxiety using the Spielberger State-Trait Anxiety Inventory (STAI-S) after 28 days.45 The study reported no statistically significant differences between groups (reported mean between-group difference, 1.83; 95% CI, -0.092 to 3.746). The second RCT evaluated intranasal midazolam compared with placebo using several scales including the Hospital Anxiety and Depression Scale, the COVI anxiety scale, and an 11-point numeric rating scale.57 Although specific data were not reported, the authors did report no difference between arms.

We concluded that anxiolytics were not more effective than placebo in treating anxiety in advanced cancer patients with dyspnea (SOE: Low).

Drug-Drug Comparisons

No drug versus drug comparisons reported on anxiety.

Health-Related Quality of Life

Placebo-Controlled Comparisons

Corticosteroids Versus Placebo

One RCT with low risk of bias evaluated oral dexamethasone versus placebo in patients with advanced cancer, assessing quality of life using the EORTC QLQ-C30 scale.47 Although specific data are not reported, the study found no statistically significant differences at 7 days. Because of the concern for study limitations and the imprecise results, we were unable to draw conclusions about the use of corticosteroids to improve health-related quality of life (SOE: Insufficient).
Drug-Drug Comparisons

No drug versus drug comparisons reported on health-related quality of life.

Clinical or Utilization Health Outcomes

Blood Pressure

Placebo-Controlled Comparisons

Opioids Versus Placebo

Two RCTs with low risk of bias compared fentanyl to placebo in patients with advanced cancer and reported effects on blood pressure.\textsuperscript{44, 46} Both RCTs were of exertional dyspnea with walking trials.

Based on the overall pooled results from the meta-analysis, we found no difference between opioids and placebo in the effect on blood pressure (Diastolic, calculated standardized mean difference, 0.243; 95% CI, -0.23 to 1.41, I\textsuperscript{-}squared=31.6\%) and (Systolic, calculated standardized mean difference, 0.478; 95% CI, -0.13 to 1.09, I\textsuperscript{-}squared=59\%) (Appendix C-Figure 7). There was significant heterogeneity in the systolic blood pressure findings.

Drug-Drug Comparisons

Opioids Versus Opioids

One RCT with low risk of bias compared different doses of sublingual fentanyl spray on blood pressure after completing a shuttle walk test in opioid tolerant patients.\textsuperscript{56} The RCT reported no significant change in blood pressure in patients in either arm of the trial (Diastolic, difference between beginning and end of walk, calculated standardized mean difference, 0.14; 95% CI, -0.54 to 0.81) (Systolic, difference between beginning and end of walk, calculated standardized mean difference, 0.17; 95% CI, -0.51 to 0.84).

Heart Rate

Placebo-Controlled Comparisons

Opioids Versus Placebo

Three RCTs (2 with low and 1 with high risk of bias) compared opioids to placebo in patients with advanced cancer, and reported effects on heart rate.\textsuperscript{43, 44, 46} Two RCTs compared fentanyl to placebo for exertional dyspnea, and the third compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline for incident dyspnea. Based on the pooled results of the meta-analysis, we found no significant difference between opioids and placebo in the effect on heart rate. Two meta-analyses are reported here to reflect the two placebo comparisons provided in one of the RCTs \textsuperscript{43} (calculated standardized mean difference with Charles, 2008 et al.\textsuperscript{43} saline versus nebulized hydromorphone comparison, -0.14; 95% CI, -0.57 to 0.29, I\textsuperscript{-}squared=0.0\%) (calculated standardized mean difference with Charles, 2008 et al.\textsuperscript{43} saline versus systemic hydromorphone comparison, -0.03; 95% CI, -0.46 to 0.4, I\textsupersquared=0.0\%) (Appendix C-Figures 8 and 9).
Drug-Drug Comparisons

Opioids Versus Opioids

Three RCTs (1 with low and 2 with high risk of bias) measured the effects of different doses or routes of opioids on heart rate in patients with advanced cancer. One RCT evaluated high doses versus low doses of fentanyl sublingual spray for exertional dyspnea, the second RCT evaluated the effect of oral versus subcutaneous morphine on dyspnea at rest and the third compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline for incident dyspnea. In the meta-analysis, we found no significant difference between opioids in the effect on heart rate (calculated standardized mean difference, 0.11; 95% CI, -0.3 to 0.52, I-squared=0.0%) (Appendix C-Figure 10).

Oxygen or Carbon Dioxide/Bicarbonate Levels (Oxygen Saturation)

Placebo-Controlled Comparisons

Opioids Versus Placebo

Five RCTs (1 with some concerns, 3 with low, and 1 with high risk of bias) compared opioids with placebo in patients with advanced cancer and reported on oxygen saturation. Four RCTs compared fentanyl with placebo in the treatment of exertional dyspnea. One RCT compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline in the treatment of incident dyspnea.

Based on the pooled results of the meta-analysis, we found no difference between opioids and placebo in the effect on oxygen saturation. Two meta-analyses are reported here to reflect the two placebo comparisons provided in one of the RCTs (calculated standardized mean difference with Charles, 2008 et al. saline versus nebulized hydromorphone comparison, -0.08; 95% CI, -0.43 to 0.26, I-squared=0.0%) (calculated standardized mean difference with Charles, 2008 et al. saline versus systemic hydromorphone comparison, -0.15; 95% CI, -0.5 to 0.2, I-squared=0.0%) (Appendix C-Figures 11 and 12).

Drug-Drug Comparisons

Opioids Versus Opioids

Two RCTs (1 with low and 1 with high risk of bias) compared opioids and reported oxygen saturation for patients with advanced cancer. One RCT compared high dose versus low dose fentanyl spray for exertional dyspnea and the second RCT compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline in the treatment of incident dyspnea.

Based on the pooled results of the meta-analysis, we found no difference in the effect on oxygen saturation (calculated standardized mean difference, 0.02; 95% CI, -0.44 to 0.48, I-squared=0.0%) (Appendix C-Figure 13).

Opioids Versus Anxiolytics

Two RCTs (1 with some concerns and 1 with high risk of bias) evaluated opioids and anxiolytics and reported oxygen saturation as an endpoint. One RCT randomized patients to receive either oral morphine or oral midazolam. The study found no significant differences in
oxygen saturation between the morphine or midazolam groups at either 90 minutes (calculated standardized mean difference, 0.001; 95% CI, -0.49 to 0.5) or day 5 (calculated standardized mean difference, -0.003; 95% CI, -0.5 to 0.49).

Second RCT evaluated opioids and anxiolytics, patients with severe dyspnea were randomized to three groups. Group M₀ received around the clock morphine with rescue midazolam, group M₁ received around the clock midazolam with rescue morphine, and group MM received around the clock morphine and midazolam with rescue morphine. The study found no significant differences for inter-group or intra-group comparisons in oxygen saturation at baseline, 24 hours, or 48 hours. No variability was reported and so we were unable to calculate a standardized mean difference.

**Respiratory Rate**

**Placebo-Controlled Comparisons**

**Opioids Versus Placebo**

Four RCTs (3 with low and 1 with high risk of bias) reported effects of opioids compared with placebo on respiratory rate in patients with advanced cancer.⁴³, ⁴⁴, ⁴⁶, ⁴⁸ Three RCTs compared fentanyl with placebo in the treatment of exertional dyspnea. The fourth study compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline in the treatment of incident dyspnea.

Based on the overall pooled results of three RCTs, we found no difference between opioids and placebo in the effect on respiratory rate. Two meta-analyses are reported here to reflect the two placebo comparisons provided in one of the RCTs ⁴³ (calculated standardized mean difference with saline versus nebulized hydromorphone comparison, 0.06; 95% CI, -0.36 to 0.49, I-squared=13.7%) (calculated standardized mean difference with saline versus systemic hydromorphone comparison, -0.00; 95% CI, -0.43 to 0.43, I-squared=16.1%) (Appendix C-Figures 14 and 15).

**Drug-Drug Comparisons**

**Opioids Versus Opioids**

Three RCTs (1 with some concerns, 1 with low, and 1 with high risk of bias) reported effects of different opioid regimens on respiratory rate in patients with advanced cancer.⁴³, ⁵⁴, ⁵⁶ One RCT randomly assigned patients to receive 25 percent of their four-hour opioid dose or to receive 50 percent of their four-hour opioid dose. One RCT compared high dose versus low dose fentanyl spray for exertional dyspnea and the third RCT compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline in the treatment of incident dyspnea.

Based on the overall pooled results of two RCTs, we found no difference between opioids in the effect on respiratory rate (calculated standardized mean difference, -0.25; 95% CI, -0.71 to 0.21, I-squared=0.0%) (Appendix C-Figure 16).

One RCT ⁵⁴ was not included in the meta-analysis as data were presented in figures and we were unable to calculate a between-group standardized mean difference. In that RCT, both groups demonstrated a statistically significant within-group reduction in mean respiratory frequency after administration of the supplementary dose.
Objective Measure of Functional Capacity

Placebo-Controlled Comparisons

Opioids Versus Placebo

Three RCTs (1 with some concerns and 2 with low risk of bias) reported outcomes in terms of distance in a six-minute walk test. All three RCTs compared fentanyl with placebo for the treatment of exertional dyspnea. In a pooled analysis of two RCTs, we found no differences in six-minute walk distance for opioids compared with placebo (calculated standardized mean difference, 0.13; 95% CI, -0.46 to 0.72, I-squared=0.0%) (Figure 6).

One RCT could not be included in the meta-analysis, as the data was reported as medians, rather than means. In this RCT, patients were randomized to receive either oral transmucosal fentanyl followed by placebo or placebo followed by transmucosal fentanyl prior to each six-minute walk test. This RCT found no significant difference in distance for the six-minute walk test regardless of the sequence they received the transmucosal fentanyl (p=0.655). We concluded that opioids were not more effective than placebo for improving functional capacity (SOE: Moderate).

Figure 6. Meta-analysis of the effects on functional capacity measures in randomized controlled trials comparing opioids with placebo in patients with advanced cancer

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study size</th>
<th>Favors intervention</th>
<th>Favors control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hui, 2014 6MWT Second Walk test, not specified time</td>
<td>20</td>
<td>0.20 (-0.68, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Hui, 2016 6MWT Second Walk, 20 minutes</td>
<td>24</td>
<td>0.08 (-0.72, 0.88)</td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.841)</td>
<td></td>
<td>0.13 (-0.46, 0.72)</td>
<td></td>
</tr>
</tbody>
</table>

Blue dot size=corresponds to study size.
Length of the bar=corresponds to range of confidence interval.
Blue diamond=the result when all of the individual studies are combined together and averaged

Drug-Drug Comparisons

No drug versus drug comparisons reported on functional capacity.
Table 13. Summary of findings for the effects of pharmacological interventions on clinical utilization health outcomes in patients with advanced cancer

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>Number of Studies Reporting Outcome (N)</th>
<th>Findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid vs. placebo</td>
<td></td>
<td>2 RCTs (N=44)</td>
<td>Pooled analysis:</td>
<td>There was no difference between opioids and placebo in the effect on blood pressure</td>
</tr>
<tr>
<td>Fentanyl vs. placebo (2)</td>
<td></td>
<td></td>
<td>• Diastolic, SMD: 0.243; 95% CI, -0.23 to 1.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Systolic, SMD: 0.478; 95% CI, -0.13 to 1.09</td>
<td></td>
</tr>
<tr>
<td>Opioid vs. opioid</td>
<td></td>
<td>1 RCTs (N=30)</td>
<td>• Diastolic, difference between beginning and end of walk, calculated SMD: 0.14; 95% CI, -0.54 to 0.81</td>
<td>There was no significant change in blood pressure in patients in either arm</td>
</tr>
<tr>
<td>High dose vs. low dose fentanyl</td>
<td></td>
<td></td>
<td>• Systolic, difference between beginning and end of walk, calculated SMD: 0.17; 95% CI, -0.51 to 0.84</td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids vs. placebo</td>
<td></td>
<td>3 RCTs (N=64)</td>
<td>Pooled analysis with Charles, 2008 et al. saline vs. nebulized hydromorphone comparison:</td>
<td>There was no significant difference between opioids and placebo in the effect on heart rate.</td>
</tr>
<tr>
<td>Fentanyl vs. placebo (2)</td>
<td>Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)</td>
<td></td>
<td>• SMD: -0.14 (95% CI: -0.57 to 0.29),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• I-squared=0.0%, p=0.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled analysis with Charles, 2008 et al. saline vs. systemic hydromorphone comparison:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• SMD: -0.03 (95% CI: -0.46 to 0.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• I-squared=0.0%, p=0.46</td>
<td></td>
</tr>
<tr>
<td>Opioid vs. opioid</td>
<td></td>
<td>3 RCTs (N=75)</td>
<td>Pooled analysis:</td>
<td>There was no significant difference between opioids in the effect on heart rate</td>
</tr>
<tr>
<td>Sublingual vs. subcutaneous morphine (1)</td>
<td>High dose vs. low dose fentanyl (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)</td>
<td></td>
<td>• SMD: 0.11; 95% CI, -0.3 to 0.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• I-squared=0.0%, p=0.79</td>
<td></td>
</tr>
<tr>
<td><strong>Oxygen saturation</strong></td>
<td></td>
<td>5 RCTs (N=97)</td>
<td>Pooled analysis with Charles, 2008 et al. saline vs. nebulized hydromorphone</td>
<td>There was no difference between opioids and placebo in the effect on oxygen</td>
</tr>
<tr>
<td>Outcome</td>
<td>Comparison</td>
<td>Number of Studies Reporting Outcome (N)</td>
<td>Findings</td>
<td>Conclusion</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------</td>
<td>-----------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
</tbody>
</table>
|         | placebo (4) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1) |                                            | comparison:  
  - SMD: -0.08 (95% CI: -0.43 to 0.26),  
  - I-squared=0.0%, p=0.51  
  Pooled analysis with Charles, 2008 et al. saline vs. systemic hydromorphone comparison:  
  - SMD: -0.15 (95% CI: -0.5 to 0.2)  
  - I-squared=0.0%, p=0.5 | saturation. |

**Respiratory rate**

| Opioid vs. placebo | Fentanyl vs. placebo (3) Hydromorphone (nebulized) vs. hydromorphone (Oral or subcutaneous) vs. placebo (nebulized) (1) | 4 RCTs (N=84) | Pooled analysis with Charles, 2008 et al. saline vs. nebulized hydromorphone comparison:  
  - SMD: 0.06 (95% CI: -0.36 to 0.49),  
  - I-squared=13.7%, p=0.32  
  Pooled analysis with Charles, 2008 et al. saline vs. systemic hydromorphone comparison:  
  - SMD: -0.00 (95% CI: -0.43 to 0.43)  
  - I-squared=16.1%, p=0.31 | There was no difference between opioids and placebo in the effect on respiratory rate. |
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>Number of Studies Reporting Outcome (N)</th>
<th>Findings</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Opioid vs. opioid | Low dose vs. high dose opioid (drug unspecified) (1) High dose vs. low dose fentanyl (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1) | 3 RCTs (N=88) | Pooled analysis:  
• SMD: -0.25; 95% CI, -0.71 to 0.21  
• I-squared=0.0%, p=0.7 | • There was no difference between opioids in the effect on respiratory rate |

SMD: standardized mean difference, RR: relative risk, MBGD: mean between group difference; vs= versus
KQ3. What are the comparative benefits of non-pharmacological, pharmacological, and multimodal interventions for improving dyspnea in patients with advanced cancer?

Key Points

- Evidence was insufficient to determine the effectiveness of combinations of non-pharmacological and pharmacological interventions, or the comparative effectiveness of nonpharmacological compared with pharmacological interventions.

Description of Included Studies

One single center RCT (some concerns in at least one risk of bias tool domain)\(^{58}\) enrolled 173 patients with advanced non-small cell lung cancer or mesothelioma, and baseline dyspnea. Participants were randomized to acupuncture alone (complementary and alternative medicine), morphine alone (opioids), or a combination of both. The study was conducted in the outpatient setting, with a primary followup of 4 hours and last followup of 14 days. This RCT was supported by government and nonprofit funding. The characteristics of the study, participants, and interventions are listed in Appendix D—Evidence Tables 3, 6, 11, 12 and 15.

Outcomes

Patient- or Caregiver-reported, or Observational Symptom-related Outcomes

Dyspnea

We found no significant difference in dyspnea scores between arms, for either the VAS (calculated standardized mean difference, 0.16; 95% CI, -0.25 to 0.56 for morphine versus acupuncture, and calculated standardized mean difference, 0.08; 95% CI, -0.31 to 0.47 for acupuncture and morphine versus acupuncture) or the Borg Scale (calculated standardized mean difference could not be calculated, \(p=0.247\) at 4 hours). Because of the concern for study limitations and the imprecise results, we were unable to draw any firm conclusions from this single study (SOE: Insufficient).

Anxiety

We found no significant differences at two weeks between any of the arms for either the Line Analogue Rating (unable to calculate standardized mean difference) or Hospital Anxiety and Depression Scale (calculated standardized mean difference, 0.13; 95% CI, -0.28 to 0.53 for morphine versus acupuncture, and calculated standardized mean difference, \(-0.10\); 95% CI, \(-0.49\) to 0.29 for acupuncture and morphine versus acupuncture).

Early improvement in anxiety was noted in both the acupuncture alone arm and the combined acupuncture and morphine arm, as compared with the morphine only arm, on the Line Analogue Rating scale. This was statistically significant at 4 hours \((p=0.022)\) but not at 14 days \((p=0.39)\).
(unable to calculate standardized mean difference). The RCT did not report early measures of anxiety or the statistical significance at 14 days using the Hospital Anxiety and Depression Scale. Because of the concern for study limitations and the imprecise results, we were unable to draw any firm conclusions from this single study (SOE: Insufficient).

Health-Related Quality of Life

In the same RCT, health-related quality of life was measured using the EORTC QLQ. Acupuncture was associated with statistically significant improvement in quality of life compared with morphine (timing not reported; calculated standardized mean difference, -0.53; 95% CI, -0.94 to -0.11). No statistically significant difference in quality of life was seen between morphine and combined acupuncture and morphine (calculated standardized mean difference, -0.29; 95% CI, -0.68 to 0.10). Because of the concern for study limitations and the imprecise results, we were unable to draw any firm conclusions from this single study (SOE: Insufficient).

Clinical or Utilization Health Outcomes

The RCT did not evaluate any of these outcomes.

Table 14. Summary of key results for the effects of non-pharmacological, pharmacological, and multimodal interventions on dyspnea, anxiety, and health-related quality of life in patients with advanced cancer

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Number of studies reporting outcome (N)</th>
<th>Findings</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids vs. acupuncture vs. combination</td>
<td>Dyspnea</td>
<td>1 RCT (N=173)</td>
<td>No significant differences between groups</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td>We were unable to draw any conclusions</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td></td>
<td></td>
<td>No significant differences at the final time point between</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

RCT = randomized controlled trial
KQ4. What are the harms of non-pharmacological and pharmacological interventions for improving dyspnea in patients with advanced cancer?

Key points

Non-pharmacological Interventions
- NPPV was associated with equipment discomfort/distress in some participants, leading to dropouts in some participants.
- Activity and rehabilitation interventions often led to fatigue and soreness, which were not associated with dropouts.
- Respiratory training interventions, such as inspiratory muscle training, could lead rarely to central nervous system symptoms (such as headache or dizziness) related to hypercapnia. These also did not lead to dropouts.
- Local symptoms from acupressure, such as local sensitivity, ecchymosis, pain at site of acupressure, were uncommon but led to dropouts in a small percentage of patients.

Pharmacological Interventions
- For central nervous system adverse effects, corticosteroids had lower rates of drowsiness compared with placebo or opioids but results for dizziness were inconsistent.
- For gastrointestinal adverse effects, opioids had higher rates of constipation compared with steroids.
- Adverse effects led to dropouts in a small percentage of patients for all types of pharmacological interventions.
- We were unable to draw conclusions for other adverse effects for opioids or other interventions, and most studies were short-term, numbers of patients were small, and many studies did not report comparisons of adverse effects.

Nonpharmacological Compared with Pharmacological
- We were unable to draw conclusions regarding the harms of nonpharmacological interventions compared with pharmacological interventions.

Non-pharmacological Interventions

Description of Included Studies
Four RCTs addressed physical harms associated with non-pharmacological interventions in patients with advanced cancer.25, 26, 31, 37. Two RCTs evaluated NPPV25, 26 with followup of 2 hours to 48 hours. One RCT each assessed activity and rehabilitation (12-week followup)31 and acupressure (4-week followup).37 The characteristics of the studies, populations, and interventions are listed in Appendix D-Evidence Tables 1, 4, 7, 8 and 13.
Patient-centered adverse effects of dyspnea treatments

We present adverse events by the type of intervention. Details of the adverse effects reported in each study can be found in Appendix D-Evidence Tables 30 to 40.

Respiratory Interventions

Two RCTs evaluating NPPV in an inpatient setting for patients with advanced cancer reported equipment discomfort/distress, insomnia, and gastrointestinal harms.25, 26

One RCT evaluated BPAP compared with high flow oxygen for 2 hours.25 Adverse events were reported on a continuous numeric rating scale for each symptom. The only adverse event that was significantly different between arms was insomnia, favoring the high flow oxygen arm (on a 0-10 scale, median change in oxygen arm, -6; median change in BPAP arm, 0; between arm p=0.02). There were no other significant between-group differences in adverse events (including equipment discomfort/distress and gastrointestinal harms).

BPAP was compared with supplemental oxygen for 48 hours in another RCT26. The study found no statistically significant differences in adverse events between arms. The calculated RR (oxygen arm compared with the BPAP arm) for each class of adverse event was the following: equipment discomfort/distress, 0.42 (95% CI, 0.17 to 1.05); central nervous system symptoms, 2.94 (95% CI, 0.12 to 71.3); dry mouth, 0.16 (95% CI: 0.02 to 1.33); gastrointestinal symptoms, 1.09 (95% CI: 0.46 to 2.57); pruritus, 0.49 (95% CI: 0.05 to 5.32); and urinary retention, 4.90 (95% CI: 0.24 to 100.83).

Activity and Rehabilitation Interventions

One RCT evaluated inspiratory muscle training compared with usual care in patients with advanced cancer for 12 weeks and reported equipment discomfort/distress and central nervous system harms.31 The rate of discomfort/distress (fatigue, chest muscle soreness) (calculated RR, 24 (95% CI: 1.50 to 383.26) and central nervous system symptoms (attributed to hypercapnia) (calculated RR, 8.64 (95% CI: 0.49 to 152.01), were more common in the intervention arm. None of these led to dropouts.

Complementary and Alternative Medicine

In one RCT, 2 of 38 (5%) participants undergoing acupressure over four weeks experienced equipment discomfort/distress (local sensitivity, ecchymosis, pain at site of acupressure) leading to treatment discontinuation. The control arm (usual care) had no such events. The calculated RR for equipment discomfort/distress was not statistically significant, 5.0 (95% CI: 0.25 to 100.80).37

Dropouts

The rates of dropout and details are presented in Appendix C (Table 1). The range of dropouts was 23 to 33 percent for activity and rehabilitation interventions (followup of 6 to 12 weeks), 23 to 69 percent for behavioral/psychoeducational interventions (followup 30 days to 12 months), 2 to 30 percent for complementary and alternative medicine interventions (followup 1 week to 11 weeks), 6 to 23 percent for respiratory interventions (followup 2 hours to 48 hours), and 19 to 41 percent for multicomponent interventions (followup 2 to 12 weeks). Overall, rates of dropouts were high. Most dropouts were due to death or clinical deterioration and not related to
study interventions. The reasons for dropouts was not reported in some RCTs.

Pharmacological Interventions

Description of Included Studies

Fourteen studies (12 RCTs and 2 retrospective studies) addressed the adverse effects and dropouts associated with pharmacological interventions (Appendix-C, Table 2). No study reported harms of opioids compared with opioids. None of these studies reported on headaches or opioid use disorder. The characteristics of the studies, participants, and interventions are listed in Appendix D-Evidence Tables 2, 5, 9, 10 and 14. We present results by adverse effect category. Details of the adverse events reported in each study can be found in Appendix D-Evidence Tables 51 to 73. The dropout results are summarized in Tables 15.

Patient-centered Adverse Effects of Dyspnea Treatments

Central Nervous System (cognitive changes, dizziness, drowsiness, fatigue, headache, respiratory depression)

Placebo-Controlled Comparisons

Opioids Versus Placebo

Three RCTs\(^44, 46, 48\) assessed central nervous system adverse effects of opioids compared with placebo in patients with advanced cancer (all fentanyl with different routes of administration, and of exertional dyspnea, with comparisons after a second walk test).

One RCT\(^46\) reported on cognitive changes with neurocognitive testing and found no significant changes in either the fentanyl or placebo arms.

Two RCTs\(^44, 46\) reported on dizziness. The meta-analysis for fentanyl compared with placebo showed no statistically significant difference between arms, with RR of 0.68 (95% CI: 0.15 to 3.11, I-squared=0.0%; p=0.41) (Appendix C-Figure 17).

All three RCTs reported on drowsiness. One RCT\(^46\) had a calculated RR for drowsiness of 0.5 (95% CI: 0.05 to 4.81) and one RCT\(^44\) had a calculated RR for increased drowsiness of 0.24 (95% CI: 0.01 to 4.44) for fentanyl compared with placebo. We were able to conduct a meta-analysis for these two RCTs, with no statistically significant difference between arms; the calculated RR was 0.38 (95% CI: 0.06 to 2.27, I-squared=0.0%; p=0.70) (Appendix C-Figure 18).

One RCT\(^48\) reported the median drowsiness score in the fentanyl arm was 0 (interquartile range, -0.75 to 0) and in the placebo arm was 0 (interquartile range, -3.25 to 0); the reported data were insufficient to calculate a standardized mean difference.

All three RCTs reported on fatigue. The meta-analysis showed no statistically significant difference between groups, mean between-group difference: standardized mean difference: -0.15 (95% CI: -0.64 to 0.34, I-squared = 0.0%, p = 0.669) (Appendix C-Figure 19).

We were unable to draw conclusions about central nervous system side effects with opioids compared with placebo.
**Anxiolytics Versus Placebo**

One RCT of midazolam compared with placebo\(^5\) reported dizziness and drowsiness only overall (not by study arm). We were unable to draw conclusions about central nervous system side effects with anxiolytics compared with placebo.

**Corticosteroids Versus Placebo**

One RCT of dexamethasone compared with placebo for dyspnea\(^4\) reported drowsiness and fatigue. The study found a significantly higher mean change in the dexamethasone arm compared with placebo for drowsiness at day 7 (standardized mean difference, -1.1; 95% CI, -1.78 to -0.41). No significant difference was seen between groups for fatigue (standardized mean difference, -0.54; 95% CI, -1.19 to 0.10). Central nervous system side effects with corticosteroids compared with placebo were inconsistent.

**Drug-Drug Comparisons**

**Opioids Versus Opioids**

Three RCTs assessed central nervous system adverse effects of opioids compared with opioids in patients with advanced cancer\(^5\)\(^3\), \(^5\)\(^6\), \(^5\)\(^9\) (two for cognitive changes, one for dizziness, three for drowsiness, and one for fatigue).

One RCT compared high dose with low dose fentanyl for exertional dyspnea measured cognitive changes using neurocognitive testing. Only one of four types of testing had a significant difference between high and low dose (calculated standardized mean difference, -0.79 (95% CI: -1.49 to -0.09)\(^5\)\(^6\) Another RCT\(^5\)\(^9\) reported cognitive changes only overall (not by study arm).

One RCT\(^5\)\(^6\) had a calculated RR for high versus low dose opioids dizziness of 0.26 (95% CI: 0.03 to 1.98) and a calculated RR for drowsiness of 2.62 (95% CI: 0.27 to 25.81). One RCT\(^5\)\(^3\) reported drowsiness (as sedation) as median only, so a standardized mean difference could not be calculated. One RCT\(^5\)\(^9\) reported drowsiness only overall (not by study arm).

One RCT\(^5\)\(^6\) had a standardized mean difference between groups (for the difference between beginning and end of walk) for fatigue of -0.53 (95% CI: -1.22 to 0.15).\(^5\)\(^6\)

We were unable to draw conclusions about central nervous system side effects for opioid versus opioid comparisons.

**Opioids Versus Anxiolytics**

One RCT of morphine compared with midazolam for dyspnea in patients with advanced cancer reported on cognitive changes (cognitive disturbance) and drowsiness (somnolence).\(^5\)\(^1\) The study found no significant difference between groups for cognitive changes; the calculated RR for midazolam compared with morphine was 2.91 (95% CI: 0.12 to 68.66). The study had no significant difference between groups for drowsiness (p=0.53); the calculated RR for midazolam compared with morphine was 1.16 (95% CI: 0.72 to 1.87). We were unable to draw conclusions about central nervous system side effects for opioid compared with anxiolytics.

**Opioids Versus Anxiolytics Versus Combination**

One RCT comparing morphine with midazolam versus a combination for breakthrough dyspnea in patients with advanced cancer reported cognitive changes (hallucinations), and
dizziness and drowsiness (reported as somnolence). The calculated RR for cognitive changes was 1.60 (95% CI, 0.68 to 3.63) for midazolam compared with morphine and 0.49 (95% CI, 0.04 to 5.50) for midazolam compared with the combination. The calculated RR for dizziness was 0.35 (95% CI: 0.01 to 8.37) for morphine versus both of the other two groups (no events in either of the other two groups). No significant differences were seen for any levels of severity for somnolence. We were unable to draw conclusions about central nervous system side effects for opioid compared with anxiolytic comparisons.

**Opioids Versus Corticosteroids Versus Bronchodilators**

One retrospective cohort study comparing morphine, methylprednisolone or aminophylline for dyspnea in patients with advanced cancer reported on dizziness and drowsiness (as somnolence). The calculated RR for dizziness was 0.03 (95% CI: 0 to 0.45) for methylprednisolone or aminophylline compared with morphine (zero events in the methylprednisolone or aminophylline groups). For drowsiness, the calculated RR for methylprednisolone or aminophylline was 0.01 (95% CI, 0.00 to 0.14) compared with morphine (zero events in the methylprednisolone or aminophylline groups).

**Gastrointestinal (Constipation, Nausea, Vomiting)**

**Placebo-Controlled Comparisons**

**Opioids Versus Placebo**

Four RCTs reported gastrointestinal adverse effects for opioids (all fentanyl) compared with placebo in patients with advanced cancer (one for diarrhea and three for nausea).

One RCT reported on diarrhea, but RR could not be calculated [2 (18%) events in both groups].

An RCT reporting on nausea had a mean change from baseline of -0.1 (standard deviation, 1.0) in the fentanyl group compared with -0.4 (standard deviation, 1.0) in the placebo group, and another RCT had a mean change for nausea from baseline of 0 (standard deviation, 0) in the fentanyl compared to -0.2 (standard deviation, 0.6) in the placebo group (all on a 10-point scale, no statistics reported for either study, standardized mean difference could not be calculated). One RCT had zero gastrointestinal events in either group.

**Corticosteroids Versus Placebo**

One RCT comparing dexamethasone with placebo in patients with advanced cancer reported on diarrhea and nausea. For diarrhea, one (7.1%) event was reported in the dexamethasone group versus none in the placebo group (calculated RR, 0.12 95% CI: 0.01 to 2.02). For nausea, there were no events in the dexamethasone group versus four (26.7%) events in the placebo group (calculated RR, 0.12 95% CI: 0.01 to 2.02).

**Drug-Drug Comparisons**

**Opioids Versus Opioids**

Three studies reported on nausea in patients with advanced cancer receiving opioids to reduce dyspnea. One RCT of high dose versus low dose fentanyl reported no significant
difference between groups (p value not significant) and one RCT of subcutaneous versus nebulized morphine\textsuperscript{53} reported no significant difference (p=0.32) (mean differences not reported for either study). One retrospective cohort of oxycodone versus hydrocotarnine\textsuperscript{59} reported only overall events.

**Opioids Versus Anxiolytics**

One RCT of midazolam versus morphine\textsuperscript{51} in patients with advanced cancer reported on both constipation and nausea. For constipation (Grade 2), the calculated RR was 0.19 (95% CI: 0.01 to 3.88) for midazolam compared with morphine.\textsuperscript{51} For moderate nausea, the calculated RR was 0.32 (95% CI, 0.01 to 7.65) for midazolam compared with morphine (p not significant).\textsuperscript{51}

**Opioids Versus Corticosteroids Versus Bronchodilators**

One retrospective cohort reported on constipation for morphine compared with methylprednisolone or aminophylline in patients with advanced cancer.\textsuperscript{55} The calculated RR was 0.01 (95% CI: 0 to 0.15) for both the methylprednisolone and aminophylline groups compared with morphine (no events in the methylprednisolone or aminophylline groups).

**Opioids Versus Anxiolytics Versus Combination**

One RCT of morphine versus midazolam versus morphine with midazolam in patients with advanced cancer\textsuperscript{52} reported on nausea/vomiting. The calculated RR for grade 2 nausea/vomiting was 0.33 (95% CI, 0.01 to 7.90) for the combination compared with midazolam, and 0.12 (95% CI, 0.01 to 2.10) for the combination compared with morphine.

**Pruritus**

**Placebo-Controlled Comparisons**

**Opioids Versus Placebo**

Two RCTs\textsuperscript{44, 48} of fentanyl compared with placebo in patients with advanced cancer reported on pruritis. One RCT\textsuperscript{44} reported a mean change of -0.3 (standard deviation, 1.0) versus 0.3 (standard deviation, 0.7) on a 10-point scale for fentanyl versus placebo (standardized mean difference could not be calculated), and one RCT\textsuperscript{48} did not report values for change but had no significant between-group difference (p=0.15).

**Drug-Drug Comparisons**

**Opioids Versus Opioids**

Two RCTs \textsuperscript{56, 59} comparing opioids with opioids in patients with advanced cancer reported on pruritus as an adverse event. One RCT of high versus low dose fentanyl\textsuperscript{56} reported a mean change of 0.1 (standard deviation, 0.2) in the high dose compared with 0 (standard deviation, 0) in the low dose on a 0-10 scale (0.43; 95% CI, 0.01 to 4.44). One retrospective cohort of oxycodone with hydrocotarnine\textsuperscript{59} reported only overall results.

**Opioids Versus Anxiolytics**

One RCT comparing morphine with midazolam in patients with advanced cancer had a calculated RR of 0.32 for pruritus (95% CI, 0.01 to 7.63) for midazolam compared with
morphine (nonsignificant between-group difference, p value not reported).  

**Urinary Retention, Dry Mouth**

**Placebo-Controlled Comparisons**

No placebo-controlled comparisons studies reported on urinary retention or dry mouth as an adverse event.

**Drug-Drug Comparisons**

**Opioids Versus Opioids**

One study of oxycodone compared with hydrocotarnine reported only on overall rates of urinary retention.  

**Opioids Versus Anxiolytics**

One RCT compared morphine versus midazolam for dyspnea in 63 patients with advanced cancer and reported one case of dry mouth for the morphine group and nonsignificant differences between groups (RR, 0.32 95% CI: 0.01 to 7.63).  

**Opioids Versus Anxiolytics Versus Combination**

One RCT compared morphine versus midazolam with morphine and midazolam together reported on dry mouth. The calculated RR was 0.35 (95% CI: 0.01 to 8.37) for morphine plus midazolam or midazolam alone compared with morphine (the only group with an event).

**Opioids Versus Corticosteroids Versus Bronchodilators**

One retrospective cohort comparing methylprednisolone, aminophylline and morphine in patients with advanced cancer reported on dry mouth. The calculated RR was 0.09 (95% CI: 0.01 to 1.68) for the methylprednisolone and aminophylline groups compared with the morphine group (the only group with events).

**Dropouts**

The rate of dropouts due to adverse effects was reported in five studies. The rates are listed in Table15.
Table 15. Rate of dropouts due to adverse effects of pharmacological interventions for dyspnea in patients with advanced cancer

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Intervention</th>
<th>Dropouts due to adverse effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Fentanyl[^44]</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone[^43]</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Morphine[^31]</td>
<td>3.2%</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>Midazolam[^51]</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td>Buspirone[^45]</td>
<td>4.7%</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone[^47]</td>
<td>5.6 – 7.1%</td>
</tr>
</tbody>
</table>

Non-pharmacological Compared with Pharmacological Interventions

One RCT (173 patients) compared opioids versus acupuncture versus a combination of both in patients with advanced cancer.[^58] The RCT did not report specific adverse effects and reported no deaths because of the intervention. The study had one dropout in the morphine group due to adverse effects.
Discussion

Findings in Relation to the Decisional Dilemma(s)

We identified 41 studies that assessed the benefits and harms of non-pharmacological and pharmacological treatments for dyspnea in advanced cancer. The review examined nonpharmacological interventions (including respiratory, behavioral and psychoeducational, activity and rehabilitation, complementary and alternative medicine, and multicomponent interventions), and pharmacological interventions (including opioids and anxiolytics), and combinations of these interventions.

A variety of nonpharmacological interventions were effective, particularly for the outcome of dyspnea. Airflow and cooling interventions (fans) were more effective than sham or usual care for improving dyspnea, based on two studies in the inpatient setting (SOE: Moderate). Non-invasive positive pressure ventilation was more effective than supplemental oxygen for improving dyspnea (SOE: Low) but was associated with equipment discomfort/distress in some participants, leading to dropouts in some. There was no difference in effectiveness between compressed air and supplemental oxygen (SOE: Low). Neither behavioral and psychoeducational interventions nor activity and rehabilitation interventions were more effective than usual care for improving dyspnea or health-related quality of life, although activity and rehabilitation interventions did improve functional capacity (SOE: Low).

Acupuncture/acupressure/reflexology were more effective than usual care or sham at improving dyspnea and health-related quality of life (SOE: Low). In addition, multicomponent interventions were more effective than usual care for improving dyspnea when they combined behavioral and psychoeducational interventions or activity and rehabilitation interventions, with or without complementary and alternative interventions (SOE: Low).

Opioids were not effective for the outcomes of dyspnea or functional capacity, within the limits of the identified studies mainly focusing on exertional dyspnea (SOE: Moderate). We found no differences in effectiveness between different doses or routes of administration of opioids for improving dyspnea (SOE: Low). Anxiolytics were not more effective than placebo for improving dyspnea, and opioids were not more effective than anxiolytics for improving dyspnea (SOE: Low). Evidence for the outcomes of anxiety, health-related quality of life and functional capacity was otherwise limited across interventions. The evidence was insufficient for corticosteroids and bronchodilators, and for comparisons between different types of anxiolytics or between different pharmacological interventions or between non-pharmacological and pharmacological interventions.

Regarding harms, noninvasive positive pressure ventilation was associated with equipment discomfort/distress in some participants, leading to dropouts in some. Few non-pharmacological studies reported harms or dropouts related to harms or burden of interventions. Corticosteroids had lower rates of drowsiness compared with placebo or opioids, and opioids had higher rates of constipation compared with steroids, but study sample sizes were generally too small to evaluate individual harms. Adverse effects led to dropouts in a small percentage of patients for all types of pharmacological interventions.

For pharmacologic interventions, opioids are well-known to have a variety of cognitive, gastrointestinal, anticholinergic, and other adverse effects, although a meta-analysis including patients with several advanced diseases, including cancer found that opioids did not have any clinically significant adverse respiratory effects. Longitudinal data in patients with advanced cancer has found that opioids and anxiolytics may have long-term adverse effects on functional
status and cognitive and gastrointestinal symptoms. A systematic review of adverse effects of corticosteroids in advanced cancer was unable to draw conclusions due to literature limitations, but short-term adverse effects (e.g., insomnia and anxiety) and long-term adverse effects (e.g., weight gain and infection) were common. These pharmacologic interventions have extensive labeling on adverse events and many, particularly opioids and anxiolytics, also have Food and Drug Administration black box warnings. For nonpharmacologic interventions, a recent qualitative review of non-invasive ventilation in a variety of conditions described a variety of uncomfortable effects (e.g., nasal lesions or dryness) and life-threatening complications (e.g., pneumonia).

In contrast to existing guidelines, which emphasize the use of pharmacologic interventions, particularly opioids and benzodiazepines, we found stronger evidence to support non-pharmacological as opposed to pharmacological interventions. Evidence in broader populations with advanced chronic disease does support various non-pharmacological treatments, including relaxation, reducing room temperature and humidifying air, and, elevating the head of the bed. A meta-analysis on oxygen compared with air for mildly or non-hypoxemic patients with chronic obstructive pulmonary disease did show evidence for effectiveness with a small effect size. For pharmacologic interventions, we did not find evidence to support the effectiveness of opioids. In contrast to our analysis, a previous meta-analysis of broader populations with a variety of advanced illnesses found evidence for the effectiveness of opioids with a small effect size. However, in that meta-analysis, only a few of the studies were in cancer patients, evidence was of low quality, followup was generally only 1-2 days, and few patients were already on chronic opioids. A previous meta-analysis found that the evidence for opioids for improving functional capacity was conflicting. The previous meta-analysis also found that nebulized opioids were not more effective than nebulized saline. Evidence in broader populations also does not support effectiveness in reducing dyspnea for nebulized diuretics or anxiolytics.

**Strengths and Limitations**

The evidence for dyspnea in advanced cancer included studies of a wide variety of interventions, types of dyspnea, and settings. However, studies were generally small with only short-term followup of minutes to a few weeks. Outcome assessments were limited, mostly addressing dyspnea through unidimensional VAS scales rather than recommended multidimensional comprehensive tools. Few studies addressed other key outcomes of anxiety, health-related quality of life, and functional capacity. Ideally, the outcome of dyspnea for intervention studies should be a comprehensive assessment that includes not only dyspnea severity, but impact on function and health-related quality of life and the key associated symptom of anxiety. Our ability to perform meta-analyses was limited by the low number of studies on each specific type of intervention, and by incomplete reporting in some studies. Furthermore, many of the studies had some concerns of risk of bias. Adverse effects were reported as continuous variables in a few studies, with an advantage of assessing changes in symptoms already common in the advanced cancer population. On the other hand, adverse effects were reported differently or incompletely, limiting syntheses between studies, and, given the small sample sizes, specific adverse event rates when reported categorically were low. Dropouts were generally not characterized as due to adverse effects, intolerability, or burden. Since most studies were very short-term, we could not determine whether patients would use or participate in these interventions for a longer period of time.

Our review focused on patients with advanced cancer, and findings from the broader
literature on dyspnea from other illnesses (particularly on the effectiveness of opioids, anxiolytics, and oxygen, where a broad literature exists) were not included. However, the results in patients with other illnesses may not apply similarly to the advanced cancer population. A broad literature exists on the potential harms of medications such as opioids and anxiolytics, but specific harms may differ in patients with advanced cancer due to differences in the degree of frailty. Since many patients with advanced cancer are now living longer, often for many years, the long-term impact of potential harms could be significant in this population.

Applicability

Although the evidence did not support specific conclusions for patients with lung cancer or comorbid chronic obstructive pulmonary disease, many patients in the included studies had these conditions, and the conclusions are likely to be applicable to these subpopulations. In particular, 15 of the 22 nonpharmacological studies and 7 of the 14 pharmacological studies where this was reported had more than 50% lung cancer patients. For some interventions, the available evidence focused on certain types of dyspnea (e.g., exertional dyspnea for opioids) and may not apply to episodic or chronic dyspnea or severe episodes. Studies were all short-term and many had less than a day of followup (eight of the 23 nonpharmacological studies and 5 of the 14 pharmacological studies where this was reported), and the evidence may not apply to longer-term dyspnea issues. Some interventions (e.g., BPAP, fans) were evaluated only in the inpatient or palliative care unit setting. None of the identified studies used caregiver observational outcomes, which is important for patients who cannot report, such as in the intensive care unit or at the very end of life.

Implications for Clinical Practice, Education, Research, or Health Policy

Clinical practice guidelines should be updated to be more consistent with the available evidence on the effectiveness of nonpharmacological interventions for dyspnea in patients with advanced cancer. For example, small, disposable fans can be made available in a variety of settings. Given the variety of potentially effective interventions, clinicians should consider nonpharmacological interventions that may be helpful, recognizing that patient preferences are important and intensive interventions or longer-term participation will be challenging for many patients with advanced cancer and have risk for harms. Other interventions, such as anxiolytics and corticosteroids, do not have sufficient evidence to support use for treatment of dyspnea in advanced cancer outside of patients with specific indications.

More research is needed on combined approaches with different options for patients, where different options can be tailored to patient circumstances and preferences or chosen in a stepped fashion. These patients have many other symptoms, needs and concerns, and studies should address dyspnea in this context.

Given that opioids are sometimes clinically necessary for comfort, especially when acute and severe at the end of life, but can have significant side effects, more research is needed to determine when they offer sufficient benefit to offset potential harms. Such studies should have long enough follow-up to determine the sustainability of potential benefits as well as long-term tolerability with measurement of dropout rates, which can be a signal of burden and lack of clinically meaningful effectiveness.
Conclusions

In conclusion, a variety of non-pharmacological interventions are effective for improving dyspnea in patients with advanced cancer, including fans, NPPV, acupuncture/acupressure/reflexology, and multicomponent interventions (behavioral and psychoeducational combined with activity and rehabilitation and/or complementary and alternative medicine), although some of these interventions can cause harm. Opioids and anxiolytics were not effective in improving dyspnea in patients with advanced cancer, although evidence was limited.
References


37. Dogan N, Tasci S. The Effects of Acupressure on Quality of Life and Dyspnea in Lung Cancer: A Randomized, Controlled Trial. Alternative therapies in health and medicine. 2019 Jun 1. PMID: 31221935.


Abbreviations

6MWT=6 minute walk test
Activity/Rehab=Activity and rehabilitation intervention
AHRQ=Agency for Healthcare Research and Quality
Behavioral/Psych=Behavioral and psychoeducational intervention
BPAP=Bi-level positive airway pressure
CAM=Complementary and alternative medicine
CI=Confidence interval
ECOG=Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30=European Organization for Research and Treatment Quality of Life Questionnaire
EPC=Evidence-based Practice Center
EQ-5D-3L=3-level version of EQ-5D
FACT-B=Functional Assessment of Cancer Therapy - Breast Cancer
FACT-G=Functional Assessment of Cancer Therapy General
HRQOL=Health-related quality of life
IQR=Interquartile range
KQ=Key Question
NPPV=Non-invasive positive pressure ventilation
NA=Not available
NR=Not reported
NRS=Numerical rating scale
p=p-value
RCT=Randomized clinical trial
RR=Relative risk
SD=Standard deviation
SE=Standard error
SMD=Standardized mean difference
SOE = Strength of evidence
VAS=Visual Analogue Scale