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**SYSTEMATIC REVIEW**

# **Interventions for Breathlessness in Patients With Advanced Cancer**

*In Partnership With*





## **Interventions for Breathlessness in Patients With Advanced Cancer**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
5600 Fishers Lane  
Rockville, MD 20857  
[www.ahrq.gov](http://www.ahrq.gov)

and

Patient-Centered Outcomes Research Institute  
1828 L Street, NW, Ste. 900  
Washington, DC 20036  
[www.pcori.org](http://www.pcori.org)

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**Prepared by:**

Johns Hopkins University Evidence-based Practice Center  
Baltimore, MD

**Investigators:**

Sydney M. Dy, M.D.  
Arjun Gupta, M.D.  
Julie M. Waldfogel, Pharm.D.  
Ritu Sharma, B.Sc.  
Allen Zhang, B.S.  
Josephine L. Feliciano, M.D.  
Ramy Sedhom, M.D.  
Jeff Day, M.D., M.A.  
Rebecca A. Gersten, M.D.  
Patricia M. Davidson, Ph.D., M.Ed., R.N., FAAN  
Eric B. Bass, M.D., M.P.H.



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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 healthcare 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, multi-stakeholder 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/about/epc/evidence-synthesis](http://www.effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis).

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](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an email 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](mailto:epc@ahrq.hhs.gov).

Gopal Khanna, M.B.A.  
Director  
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.  
Director  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Nakela Cook, M.D., M.P.H.  
Executive Director  
Patient-Centered Outcomes Research Institute

Jean Slutsky, P.A., M.S.P.H.  
Chief Engagement and Dissemination Officer  
Patient-Centered Outcomes Research Institute

Stephanie Chang, M.D., M.P.H.  
Director  
Evidence-based Practice Center Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D.  
Task Order Officer  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Michelle Althuis, Ph.D.  
Associate Director, Research Synthesis  
Patient-Centered Outcomes Research Institute

Ellen K. Kimmel, M.L.I.S.  
Medical Librarian/Program Officer  
Patient-Centered Outcomes Research Institute



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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:

Stephanie Abel, Pharm.D., B.C.P.S.\*  
University of Kentucky HealthCare  
Lexington, KY

Margaret Campbell, Ph.D., R.N., FPCN\*  
Wayne State University  
Detroit, MI

Andrea Ferris, M.B.A.  
LUNgevity Foundation  
Bethesda, MD

Pamela K. Ginex, Ed.D., M.P.H., B.S.N., OCN\*  
Evidence-based Practice and Inquiry Oncology Nursing Society  
Pittsburgh, PA

David Hui, M.D., M.Sc.\*  
The University of Texas MD Anderson Cancer Center  
Houston, TX

Richard A. Mularski, M.D., M.S.H.S., M.C.R., ATSF, FCCP, FACP  
Kaiser Permanente Center for Health Research



Portland, OR

Eric Roeland, M.D.\*  
Massachusetts General Hospital  
Boston, MA

Cardinale B. Smith, M.D., Ph.D.  
Mount Sinai Hospital  
New York, NY

\*Provided input on Draft 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 nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Nathan Cherny, M.D.  
Shaare Zedek Medical Center  
Jerusalem, Israel

Kavita Dharmarajan, M.D., M.Sc.  
Mount Sinai Hospital  
New York, NY

Virginia Sun, Ph.D., R.N.  
City of Hope National Medical Center  
Duarte, CA

Maxwell T. Vergo, M.D.  
Dartmouth Geisel School of Medicine  
Lebanon, NH



# Interventions for Breathlessness in Patients With Advanced Cancer

## Structured Abstract

**Objectives.** To assess benefits and harms of nonpharmacological and pharmacological interventions for breathlessness 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 May 2020.

**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: breathlessness, anxiety, health-related quality of life, and exercise capacity. We performed meta-analyses when possible and calculated standardized mean differences (SMDs).

**Results.** We included 48 RCTs and 2 retrospective cohort studies (4,029 patients). The most commonly reported cancer types were lung cancer and mesothelioma. The baseline level of breathlessness varied in severity. Several nonpharmacological interventions were effective for breathlessness, including fans (SMD -2.09 [95% confidence interval (CI) -3.81 to -0.37]) (SOE: moderate), bilevel ventilation (estimated slope difference -0.58 [95% CI -0.92 to -0.23]), acupressure/reflexology, and multicomponent nonpharmacological interventions (behavioral/psychoeducational combined with activity/rehabilitation and integrative medicine). For pharmacological interventions, opioids were not more effective than placebo (SOE: moderate) for improving breathlessness (SMD -0.14 [95% CI -0.47 to 0.18]) or exercise capacity (SOE: moderate); most studies were of exertional breathlessness. Different doses or routes of administration of opioids did not differ in effectiveness for breathlessness (SOE: low). Anxiolytics were not more effective than placebo for breathlessness (SOE: low). Evidence for other pharmacological interventions was limited. Opioids, bilevel ventilation, and activity/rehabilitation interventions had some harms compared to usual care.

**Conclusions.** Some nonpharmacological interventions, including fans, acupressure/reflexology, multicomponent interventions, and bilevel ventilation, were effective for breathlessness in advanced cancer. Evidence did not support opioids or other pharmacological interventions within the limits of the identified studies. More research is needed on when the benefits of opioids may exceed harms for broader, longer term outcomes related to breathlessness in this population.



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# Evidence Summary

## Main Points

For patients with advanced cancer:

- Airflow interventions (fans) were more effective for improving breathlessness compared with usual care or sham.
- Bilevel ventilation (a form of noninvasive positive pressure ventilation) was more effective than standard supplemental oxygen for improving breathlessness.
- Acupressure/reflexology were more effective than usual care or sham for improving breathlessness.
- Neither behavioral/psychoeducational interventions alone nor activity/rehabilitation interventions alone were more effective than usual care for improving breathlessness. However, multicomponent nonpharmacological interventions that combined these, with integrative medicine interventions, were more effective than usual care for improving breathlessness.
- Opioids were not more effective than placebo or anxiolytics for improving breathlessness or exercise capacity; most of these studies in advanced cancer were of exertional breathlessness. Studies on opioids showed no differences in effectiveness between different doses or routes of administration for improving breathlessness.
- Anxiolytics were not more effective than placebo for improving breathlessness.
- Both nonpharmacological and pharmacological interventions led to adverse event-related dropouts in a small percentage of patients.

## Background and Purpose

Breathlessness, defined as difficulty breathing or shortness of breath, is frequent in advanced cancer<sup>1</sup> and often debilitating. Acute, chronic, or exertional breathlessness can reduce ability to function and participate in desired activities<sup>2</sup> 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, nonpharmacological 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 nonpharmacological and pharmacological interventions for management of breathlessness in adults with advanced cancer.

## Methods

We followed the Agency for Healthcare Research and Quality's (AHRQ's) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.<sup>3</sup> Our protocol is posted on the AHRQ Website (<https://www.ahrq.gov/research/findings/ta/index.html>) and registered on PROSPERO (CRD42020155487). Details of our methodology can be found in the full report and methods appendix.



## Results

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

### Key Question 1. What are the comparative benefits of nonpharmacological interventions (either alone or in combination) for improving breathlessness in patients with advanced cancer?

We found 29 randomized controlled trials (RCTs) (2423 patients).

#### **Respiratory interventions (9 RCTs):**

- Airflow interventions (3 RCTs) (fans) were effective for improving breathlessness compared with usual care or sham [Meta-analysis: standardized mean difference (SMD), -2.09; 95% confidence interval (CI) -3.81 to -0.37, favoring the fan arm] (Strength of evidence (SOE): Moderate).
- Compressed air and standard supplemental oxygen (4 RCTs) did not differ for improving breathlessness (SOE: Low).
- Bilevel ventilation was more effective than supplemental oxygen for improving breathlessness [1 RCT, estimated slope difference, -0.58; 95% CI, -0.92 to -0.23, favoring bilevel ventilation] (SOE: Low). Bilevel ventilation and high flow nasal cannula (1 RCT) did not differ for improving breathlessness (SOE: Low).

#### **Behavioral/psychoeducational interventions (3 RCTs):**

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

#### **Activity/rehabilitation interventions (7 RCTs):**

- Activity/rehabilitation interventions did not improve breathlessness, or health-related quality of life, but did improve exercise capacity, more than usual care (SOE: Low).

#### **Integrative medicine interventions (4 RCTs):**

- Acupressure/reflexology were more effective than usual care or sham at improving breathlessness (SOE: Low).

#### **Multicomponent nonpharmacological interventions (behavioral/psychoeducational combined with activity/rehabilitation, and/or integrative medicine) (6 RCTs):**

- Multicomponent interventions incorporating all three intervention types were more effective for improving breathlessness compared with usual care (SOE: Low).

### Key Question 2. What are the comparative benefits of pharmacological interventions (either alone or in combination) for improving breathlessness in patients with advanced cancer?

We found 17 RCTs and 1 retrospective study (1224 patients).

- Opioids were not more effective than placebo (SOE: moderate) for improving breathlessness [Meta-analysis: SMD, -0.14; 95% CI, -0.47 to 0.18] or exercise capacity (most studies were of exertional breathlessness), and not more effective than anxiolytics for improving breathlessness (SOE: Low).



- Studies showed no difference in effectiveness between different doses or routes of administration of opioids for improving breathlessness [Meta-analysis: SMD: 0.15 (95% CI: -0.22 to 0.52)] (SOE: Low).
- Anxiolytics were not more effective than placebo for improving breathlessness (SOE: Low).
- Evidence for other pharmacological interventions was limited.

### Key Question 3. What are the comparative benefits of nonpharmacological, pharmacological, and multimodal interventions for improving breathlessness in patients with advanced cancer?

The evidence was insufficient to draw conclusions (2 RCTs, 287 patients).

### Key Question 4. What are the harms of nonpharmacological and pharmacological interventions for improving breathlessness in patients with advanced cancer?

#### **Nonpharmacological interventions:**

- Bilevel ventilation 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 numerous studies evaluating a variety of nonpharmacological and pharmacological interventions for different types of breathlessness in various settings for advanced cancer. However, sample sizes were small, followup was short term, most studies only used visual analog scales for measuring breathlessness, 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 breathlessness, all but one of the placebo-controlled studies were in short-term exertional breathlessness. 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 nonpharmacological interventions, including fans, bilevel ventilation, acupressure/reflexology, and multicomponent interventions



(behavioral/psychoeducational combined with activity/rehabilitation and integrative medicine) were effective for improving breathlessness in patients with advanced cancer. Opioids and anxiolytics were not effective, although studies were limited, and few studies evaluated other pharmacological interventions. Clinical practice guidelines that recommend opioids for breathlessness 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.

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# Introduction

## Background

Breathlessness, defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity,” is frequent in patients with advanced cancer<sup>1</sup> and often debilitating. Acute, chronic, or exertional breathlessness can reduce quality of life, functional status, and the ability to participate in desired activities.<sup>2</sup> It can be distressing for patients and caregivers. Breathlessness and anxiety are often interrelated: anxiety may masquerade as breathlessness, and breathlessness or fear of breathlessness 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.<sup>3</sup> When treatment of the clinical conditions causing breathlessness does not fully relieve symptoms or is not an option, nonpharmacological and pharmacological palliative measures can be tried to help improve symptoms. Ideally, patient-centered assessment of breathlessness should include not only breathlessness severity, but also the impact on function, quality of life, and anxiety.<sup>4</sup>

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

## Nonpharmacological Treatment

Nonpharmacological treatments potentially helpful for breathlessness include respiratory, behavioral/psychoeducational, activity/rehabilitation, and integrative medicine interventions. Respiratory interventions can include fan therapy,<sup>5</sup> water spray,<sup>6</sup> standard supplemental oxygen, compressed air, or bilevel ventilation (a form of noninvasive positive pressure ventilation).<sup>7</sup> Various behavioral or psychoeducational interventions may be used, including cognitive behavioral therapy and relaxation or distraction exercises.<sup>8</sup> Activity/rehabilitation interventions may include breathing exercises, pulmonary rehabilitation, or physical interventions such as mobility aids or exercise.<sup>9, 10</sup> Integrative medicine interventions include acupuncture, acupressure, meditation, and music therapy.<sup>9, 10</sup>

## Pharmacological Treatment

Pharmacological treatments for breathlessness 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, non-steroidal anti-inflammatory agents, or lidocaine.<sup>11</sup> Anxiolytics could help treat the symptom of breathlessness directly or indirectly (by reducing associated anxiety).

## Scope of the Review

Other types of interventions may help to reduce breathlessness when consistent with patient preferences and prognosis 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.<sup>12</sup> Other symptoms common in advanced cancer, such as pain, may interact with breathlessness, 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 breathlessness, such as anemia, pneumonia, pneumonitis, pulmonary embolism, bronchial obstruction, and pleural effusions.<sup>12</sup>

## **Purpose of the Review**

This systematic review will provide a comprehensive review of current evidence to help the American Society of Clinical Oncology to prepare a clinical practice guideline on comparative benefits and harms of pharmacological and nonpharmacological interventions for the management of breathlessness 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).<sup>13</sup>

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 website ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) and registered on PROSPERO (CRD42020155487).

## Key Questions

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

## Analytic Framework

Figure 1 displays the analytic framework for addressing the Key Questions.

## Study Selection

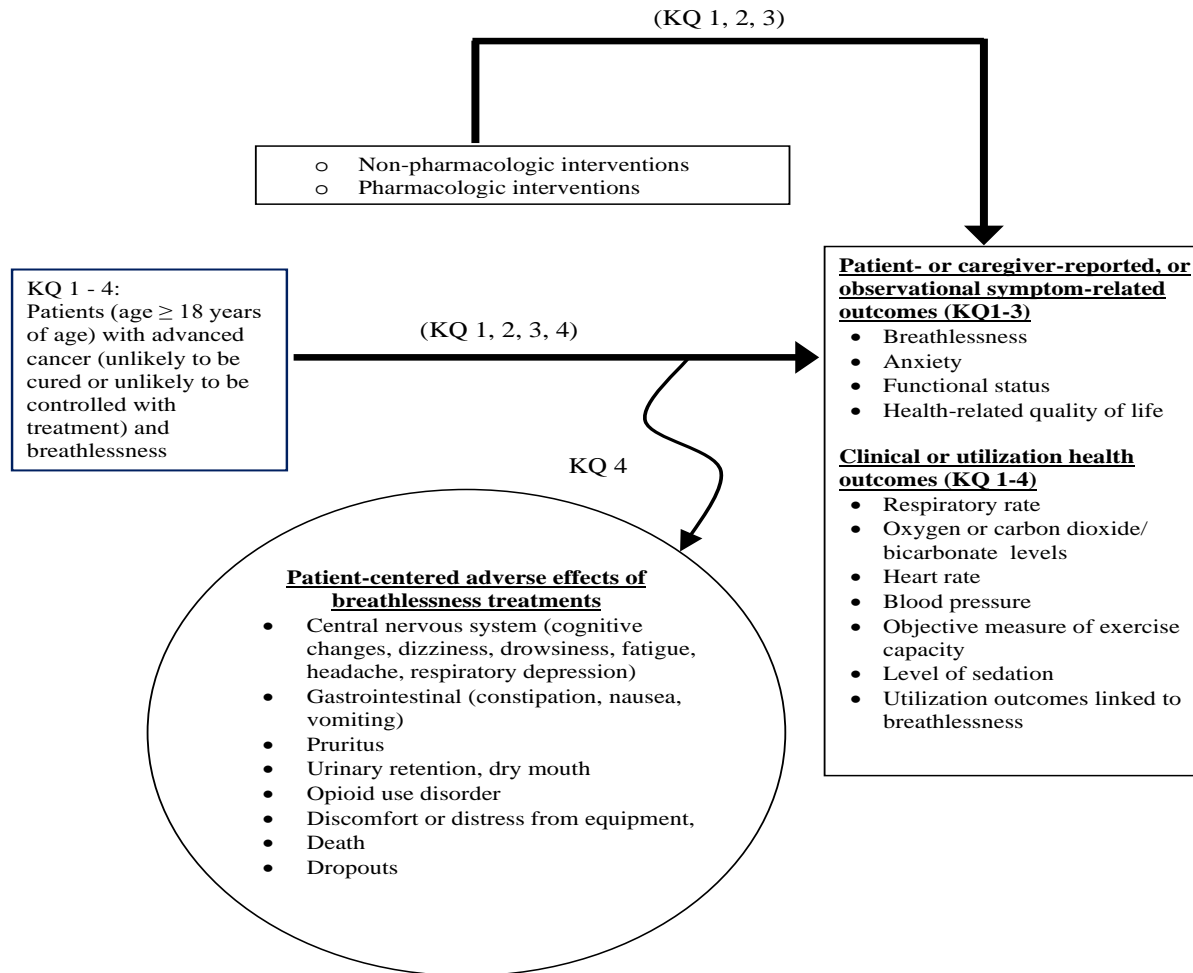
We searched the following databases for primary studies through early May 2020: PubMed, Embase®, CINAHL, ISI Web of Science, and the Cochrane Central Register of Controlled Trials. Study selection was based on predefined eligibility criteria within the framework shown in Table A-1 in the Appendix A., which lists our inclusion and exclusion criteria. Full details on the search strategy and eligibility criteria are in Appendix A and list of excluded studies at the full text level in Appendix B.

## 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).<sup>14</sup> 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).<sup>15</sup> Overall risk of bias for each study was classified as low risk of bias, some concerns, and high risk of bias. Details on the data extraction are in the Appendix A.



**Figure 1. Analytic framework for evaluating interventions for breathlessness in patients with advanced cancer**



KQ =Key Question



## 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.<sup>16</sup> 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).<sup>17</sup> We used Cohen's classification to categorize effect sizes as small, medium or large.<sup>18</sup> In a situation where dichotomous outcomes were presented, we calculated a pooled effect estimate of the relative risk 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 visual analog scale as clinically meaningful in the evaluation of effectiveness based on available standards, which is equivalent to a standardized mean difference of 0.35 (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.<sup>19</sup> 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, breathlessness, anxiety, and exercise 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 Appendix A –“Grading the Strength of the Body of Evidence”.



# Results

## Search Results

We retrieved 7729 unique citations (Appendix C, Figure C-1). After screening abstracts and full text, we included 50 studies.

Of the eligible studies, 29 randomized controlled trials (RCTs) addressed the benefits and harms of nonpharmacological interventions, 19 studies (17 RCTs and 2 retrospective studies) addressed the benefits and harms of pharmacological interventions, and two RCTs addressed the benefits and harms of nonpharmacological, pharmacological, and multimodal (nonpharmacological combined with pharmacological) interventions. We list the number of studies by type of outcome assessed in Table 1. Definitions of common terms used in the report are in Appendix A (Table A-3).

**Table 1. List of included studies by outcomes**

Key Questions	Patient- or Caregiver-Reported, or Observational Symptom-Related Outcomes	Clinical or Utilization Health Outcomes	Patient-Centered Adverse Effects of Breathlessness Treatments
Benefits and harms of nonpharmacological interventions [KQ1 and 4]	29 (29 RCTs)	17 (17 RCTs)	5 (5 RCTs)
Benefits and harms of pharmacological interventions [KQ2 and KQ4]	18 (17 RCTs, 1 retrospective study)	11 (11 RCTs)	14 (12 RCTs, 2 retrospective studies)
Benefits and harms of nonpharmacological, pharmacological, and multimodal [KQ3 and KQ4]	2 (2 RCT)	1 (1 RCT)	1 (1 RCT)

KQ =Key Question; NR=not reported; RCT =randomized controlled trial

**Key Question 1. What are the comparative benefits of nonpharmacological interventions (either alone or in combination) for improving breathlessness in patients with advanced cancer?**

## Key Points

- Airflow interventions (e.g., fans) were effective for improving breathlessness compared with usual care or sham interventions in patients with advanced cancer (Strength of evidence [SOE]: Moderate).
- Bilevel ventilation was more effective than standard supplemental oxygen for improving breathlessness 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 breathlessness, 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 were also no more effective than usual care for improving breathlessness or anxiety in patients with advanced cancer (SOE: Low).



- Integrative medicine interventions (acupressure and reflexology) were more effective than usual care or sham procedures at improving breathlessness in patients with advanced cancer (SOE: Low). We were unable to draw conclusions for music therapy (SOE: Insufficient)
- Multicomponent interventions which combined all three of behavioral/psychoeducational, activity/rehabilitation, and integrative medicine interventions were more effective for improving breathlessness compared with usual care in patients with advanced cancer (SOE: Low).

Twenty-nine RCTs (2,423 patients) addressed the benefits of nonpharmacological interventions for managing breathlessness in patients with advanced cancer. The characteristics of the studies, participants, and interventions are listed in Appendix D-Evidence Tables D-1, D-4, D-7, D-8, and D-13.
















We present results by the type of intervention - respiratory (9 RCTs), behavioral/psychoeducational (3 RCTs), activity/rehabilitation (7 RCTs), integrative medicine (4 RCTs), and multicomponent (6 RCTs). See Appendix D, Evidence Tables D-16 through D-27, for details of the outcome data.

The summary of key findings and SOE for the key outcomes are presented in Tables 2 and 3. See Appendix A for details on the methodology used to assess SOE.



















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






**Table 2. Summary of key findings for the effects of nonpharmacological interventions on breathlessness in patients with advanced cancer**

Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
<b>Respiratory interventions: Airflow vs. usual care or sham control</b>	 Improvement	 Moderate	 3 RCTs <sup>20-22</sup> N = 115	These interventions yielded a statistically significant improvement in breathlessness in the intervention arm, compared with the control arm. On meta-analyses, the SMD was -2.09 (95% CI, -3.81 to -0.37, I-squared = 94.3%) favoring the fan arm.	Fans were effective for improving breathlessness
<b>Respiratory interventions: Compressed air vs. standard supplemental oxygen</b>	 Equivalence	 Low	 4 RCTs <sup>23-26</sup> N = 96	3 RCTs reported no statistically significant between group differences. 1 RCT reported improvement in the standard supplemental oxygen arm compared with compressed air arm.	Compressed air and standard supplemental oxygen did not differ for improving breathlessness
<b>Respiratory interventions: Bilevel ventilation vs. high flow nasal cannula</b>	 Equivalence	 Low	 1 RCT <sup>27</sup> N = 30	1 RCT reported no between group differences between bilevel ventilation and high flow nasal cannula. 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.	Bilevel ventilation and high flow nasal cannula did not differ for improving breathlessness
<b>Respiratory interventions: Bilevel ventilation vs. standard supplemental oxygen</b>	 Improvement	 Low	 1 RCT <sup>28</sup> N = 189	Bilevel ventilation yielded a statistically significant improvement in breathlessness compared with standard supplemental oxygen (p=0.0012).	Bilevel ventilation was more effective in improving breathlessness compared with standard supplemental oxygen
<b>Behavioral/psychoeducational interventions vs. usual care</b>	 Equivalence	 Low	 3 RCTs <sup>29-31</sup> N = 197	2 RCTs reported no statistically significant between group differences. 1 RCT reported improvement in the intervention arm compared with the control arm (p=0.03).	Behavioral/psychoeducational interventions were not effective for improving breathlessness.



Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
Acupuncture vs. sham acupuncture	 No conclusion drawn	 Insufficient	 1 RCT <sup>32</sup> N = 33	1 RCT reported no improvement in the intervention arm compared with the control arm.	Not applicable
Acupressure/reflexology vs. sham intervention or usual care or both	 Improvement	 Low	 2 RCTs <sup>33, 34</sup> N = 206	2 RCTs reported statistically significant between group differences favoring the intervention arm.	Acupressure/reflexology is effective for improving breathlessness compared with usual care or sham procedures
Music therapy vs. control group	 No conclusion drawn	 Insufficient	 1 RCT <sup>35</sup> N = 40	Statistically significant improvement in breathlessness in the music therapy group but not in the control group. Between group differences and effect sizes were not reported.	Not applicable
Activity/rehabilitation interventions vs. activity/rehabilitation interventions (different types) or usual care	 Equivalence	 Low	 7 RCTs <sup>36-42</sup> N = 227	5 RCTs reported no statistically significant between group differences. 2 RCTs reported improvement in the intervention arm compared with the control arm.	Activity /rehabilitation interventions were not more effective than usual care for improving breathlessness
Multicomponent combined behavioral/psychoeducational and activity/rehabilitation Interventions, vs. usual care	 Equivalence	 Low	 3 RCTs <sup>43-45</sup> N = 184	2 RCTs reported a statistically significant (with small or unknown effect sizes) between group differences favoring the intervention arm. 1 RCT reported no improvement in the intervention arm compared with the control arm.	No clinically important improvement in breathlessness was seen with the interventions that combined behavioral/psychoeducational and activity/rehabilitation interventions.
Multicomponent combined behavioral/psychoeducational, activity/rehabilitation and integrative medicine interventions, vs. usual care	 Improvement	 Low	 2 RCTs <sup>46, 47</sup> N = 100	Significant improvement in breathlessness 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).	The combination of behavioral/psychoeducational, activity/rehabilitation and integrative medicine interventions was more effective for improving breathlessness than usual care.












Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
<b>Multicomponent combined behavioral/ psychoeducational and integrative medicine interventions vs. usual care</b>	 No conclusion drawn	 Insufficient	 1 RCT <sup>48</sup> N = 38	No statistically significant difference between arms.	Not applicable

CI=confidence intervals; SMD= standardized mean difference; RCT=randomized controlled trial
















\*Moderate strength indicates that further research may change the result; low strength indicates low confidence that the evidence reflects the true effect, and further research is very likely to change the result, and insufficient evidence indicates that evidence is unavailable or does not permit a conclusion.

†Dot size in each cell corresponds to number of participants in the study.


















**Table 3. Summary of key findings for the effects of nonpharmacological interventions on anxiety, exercise capacity, and health-related quality of life in patients with advanced cancer**

Outcome	Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
Anxiety	<b>Respiratory interventions: Airflow vs. usual care or sham</b>	 No conclusion drawn	 Insufficient	 1 RCT <sup>20</sup> N = 40	No statistically significant between group differences. The SMD was -0.11 (95% CI, 0-0.73 to 0.50).	Not applicable
Anxiety	<b>Acupressure/reflexology vs. sham intervention or usual care or both</b>	 No conclusion drawn	 Insufficient	 1 RCT <sup>33</sup> N = 222	No statistically significant between group differences.	Not applicable
Anxiety	<b>Music therapy vs. control group</b>	 No conclusion drawn	 Insufficient	 1 RCT <sup>35</sup> N = 40	Statistically significant improvement in anxiety in the music therapy group but not in the control group. Between group differences and effect sizes were not reported.	Not applicable








Outcome	Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
Anxiety	Activity/rehabilitation interventions vs. activity/rehabilitation interventions or usual care	 No conclusion drawn	 Insufficient	 2 RCTs <sup>36, 37</sup> N = 60	1 RCT reported no statistically significant between group differences. 1 RCT reported improvement in intervention arm compared with control arm.	Not applicable
Anxiety	Multicomponent combined behavioral/psychoeducational and activity/rehabilitation Interventions vs. usual care	 Equivalence	 Low	 3 RCTs <sup>43-45</sup> N = 212	2 RCTs reported no statistically significant between group differences. 1 RCT reported improvement in intervention arm compared with control arm.	Multicomponent combined behavioral/psychoeducational, activity/rehabilitation interventions were not effective for improving anxiety compared with usual care
Anxiety	Multicomponent combined behavioral/psychoeducational, activity/rehabilitation and integrative medicine Interventions vs. usual care	 Equivalence	 Low	 2 RCTs <sup>46, 47</sup> N = 99	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%).	Multicomponent combined behavioral/psychoeducational, activity/rehabilitation and integrative medicine interventions were not effective for improving anxiety compared with usual care
Anxiety	Multicomponent combined Behavioral/Psychoeducational and Integrative Medicine Interventions vs. usual care	 No conclusion drawn	 Insufficient	 1 RCT <sup>48</sup> N = 38	No statistically significant difference between arms.	Not applicable
Exercise capacity	Respiratory interventions: Compressed air vs. standard supplemental oxygen	 No conclusion drawn	 Insufficient	 1 RCT <sup>23</sup> N = 33	No statistically significant between group differences. The SMD was -0.11 (95% CI, 0-0.73 to 0.50).	Not applicable



Outcome	Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
Exercise capacity	Acupressure/reflexology vs. sham intervention or usual care or both	 No conclusion drawn	 Insufficient	 1 RCT <sup>34</sup> N = 60	No difference	Not applicable
Exercise capacity	Activity/rehabilitation interventions vs. activity/rehabilitation interventions or usual care	 Improvement	 Low	 3 RCTs <sup>36, 38, 39</sup> n = 72	2 RCTs reported a statistically significant difference between group differences favoring the intervention arm. 1 RCT reported a statistically significant within group improvement in the intervention arm, but not the control arm.	Activity/rehabilitation interventions improved exercise capacity.
Exercise capacity	Multicomponent combined behavioral/psychoeducational and activity/rehabilitation Interventions vs. usual care	 No conclusion drawn	Insufficient	 1 RCT <sup>45</sup> N= 62	1 RCT reported no statistically significant between group differences	Not applicable
Health-related quality of life	Behavioral/psychoeducational interventions vs. usual care	 Equivalence	 Low	 3 RCTs <sup>29-31</sup> N=197	No statistically significant between group differences.	Behavioral/psychoeducational interventions did not improve health-related quality of life compared with usual care
Health-related quality of life	Acupressure/reflexology vs. sham intervention or usual care or both	 Equivalence	 Low	 2 RCTs <sup>33, 34</sup> N=206	Meta-analysis of 2 RCTs showed no statistically significant difference between arms the SMD was -2.00 (95% CI; -5.76 to -1.76), (I-squared = 98.5%)	Acupressure/reflexology intervention did not improve health-related quality of life compared with usual care or sham procedures
Health-related quality of life	Activity/rehabilitation interventions vs. activity/rehabilitation interventions or usual care	 Equivalence	 Low	 5 RCTs <sup>36-40</sup> N=188	4 RCTs reported no statistically significant between group differences. 1 RCT reported improvement in the intervention arm compared with the control	There were no differences between different activity/rehabilitation interventions or usual care for health-related



Outcome	Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
					arm.	quality of life
Health-related quality of life	<b>Multicomponent combined behavioral/psychoeducational and activity/rehabilitation Interventions vs. usual care</b>	 No conclusion drawn	Insufficient	 1 RCT <sup>45</sup> N=62	1 RCT reported no statistically significant difference between group differences	Not applicable
Health-related quality of life	<b>Multicomponent combined behavioral/psychoeducational, activity/rehabilitation, and integrative medicine interventions vs. usual care</b>	 Equivalence	 Low	 2 RCTs <sup>46, 47</sup> N=99	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-squared = 0.0%).	Combined behavioral/psychoeducational, activity/rehabilitation, and integrative medicine interventions were not effective for improving health-related quality of life compared with usual care

CI=confidence intervals; SMD= standardized mean difference; RCT=randomized controlled trial

\*Low strength of evidence indicates low confidence that the evidence reflects the true effect, and further research is very likely to change the result, and insufficient strength of evidence indicates that evidence is unavailable or does not permit a conclusion

†Dot size corresponds to number of participants in the study.



## **Respiratory Interventions**

### **Description of Included Studies**

Nine RCTs (some concerns in at least one risk of bias tool domain) evaluated respiratory interventions for managing breathlessness in patients with advanced cancer,<sup>20-28</sup> of which six included a crossover design<sup>21-26</sup> Table 4 provides an overview of included RCTs.



**Table 4. Overview of respiratory interventions for patients with advanced cancer**

	Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
<b>Airflow (3 RCTs)</b>	Wong, 2017 <sup>21</sup>  N=30	Single-center, inpatient hospice, Asia  Lung cancer (43%), 97% on standard supplemental oxygen, baseline $\geq 3/10$ breathlessness on numeric rating scale  No funding	Usual Care: Same nursing care as in intervention arm, standard supplemental oxygen, rescue medications, posture changes as needed.  Airflow: 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.	5 minutes, then crossover
	Kako, 2018 <sup>20</sup>  N=40	Single-center, inpatient palliative care unit, Asia  Lung cancer (38%), other cancers (62%), 50% on standard supplemental oxygen, baseline $\geq 3/10$ breathlessness on numeric rating scale, Eastern Cooperative Oncology Group performance status 3-4  Government funding	Sham control: fan to legs, slowest speed to start. Other settings (distance, location, strength, swing of fan) per patient preference.  Airflow: 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.	5 minutes
	Ting, 2020 <sup>22</sup>  N=48	Single-center, inpatient, Asia  Lung cancer (21%), baseline $\geq 3/10$ breathlessness on modified Borg scale, Eastern Cooperative Oncology Group performance status 3-4  Funding not reported	Sham control: fan to unexposed legs, slowest speed to start. Other settings (distance, location, strength, swing of fan) per patient preference.  Airflow: 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.	5 minutes, then crossover



	Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
<b>Compressed Air and Standard Supplemental Oxygen (4 RCTs)</b>	Booth, 1996 <sup>24</sup>  N=38	Multi-center, inpatient hospice unit, Europe  Lung cancer and mesothelioma (58%), other cancers (42%), no prior oxygen use  Non-profit funding	Compressed air: room air by nasal cannula at 4L/minute for 15 minutes.  Standard supplemental oxygen: oxygen by nasal cannula at 4L/minute for 15 minutes.  After 15 minutes, groups underwent crossover.	15 minutes, then crossover
	Bruera, 1993 <sup>26</sup>  N=14	Single center, setting not reported, North America  Lung cancer and mesothelioma (36%), other cancers (64%), terminal patients, hypoxemic (oxygen saturation <90% on room air but oxygen needs < 4L/minute)  No funding source reported	Compressed air: room air by facemask at 5L/minute for 5 minutes.  Standard supplemental oxygen: oxygen by facemask at 5L/minute for 5 minutes.  After 5 minutes, groups underwent crossover.	5 minutes, then crossover
	Bruera, 2003 <sup>23</sup>  N=33	Single-center, outpatient, North America  Lung cancer and mesothelioma (94%), other cancers (6%), ambulatory patients, non-hypoxemic (oxygen saturation greater than or equal to 90% on room air at rest), with $\geq 3/10$ baseline breathlessness on numeric rating scale  No funding source reported	Compressed air: room air by nasal cannula set at 5L/minute. Delivered for 5 minutes, with patient at rest, followed by 6-minute walk.  Standard supplemental oxygen: oxygen by nasal cannula set at 5L/minute. Delivered for 5 minutes, with patient at rest, followed by 6-minute walk.  After 11 minutes, groups underwent crossover.	11 minutes, then crossover



	Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
	Philip, 2006 <sup>25</sup>  N=51	Multi-center, inpatient and outpatient, Australia  Lung cancer and mesothelioma (43%), other cancers (57%), baseline breathlessness $\geq$ 30/100 on visual analog scale.  Non-profit funding	Compressed air: room air by nasal cannula at 4L/minute for 15 minutes.  Standard supplemental oxygen: oxygen by nasal cannula at 4L/minute for 15 minutes.  After 15 minutes, groups underwent crossover.	15 minutes, then crossover
<b>Bilevel Ventilation (2 RCTs)</b>	Hui, 2013 <sup>27</sup>  N=30	Single-center, inpatient, North America  Lung cancer and mesothelioma (55%), other cancers (45%), Eastern Cooperative Oncology Group performance status 3-4, $\geq$ 3/10 baseline breathlessness on numeric rating scale despite standard supplemental oxygen  Government funding	High Flow Nasal Cannula: Oxygen flow of 10 to 40L/min via nasal prongs titrated to comfort. Oxygen was humidified and heated (temperature titrated between 35-37 Celsius). Oxygen set at 100%. Administered by a respiratory therapist for 2 hours.  Bilevel ventilation: Level of support started at inspiratory positive airway pressure of 8 cm H <sub>2</sub> O over expiratory positive airway pressure of 5 cm H <sub>2</sub> O. Inspiratory positive airway pressure varied between 8 to 18 cm H <sub>2</sub> O, and expiratory positive airway pressure varied between 3 to 10 cm H <sub>2</sub> O. Oxygen set at 100%. Administered by a respiratory therapist for 2 hours.	2 hours
	Nava, 2013 <sup>28</sup>  N=200	Multi-center, intensive care unit, Europe and Asia  Lung cancer and mesothelioma (40%), other cancers (60%), life expectancy < 6 months, baseline breathlessness $\geq$ 4/10 on Borg scale  No funding	Control: Standard supplemental oxygen via Venturi mask or reservoir mask (titrated to goal oxygen saturation > 90%).  Bilevel ventilation: Level of initial support, inspiratory positive airway pressure of 10 cm and expiratory positive airway pressure of 5 cm of H <sub>2</sub> O. Increased by a ratio of 2/1, with respiratory rate set at 12/minute.  Rescue therapy allowed in both arms: 10 mg of subcutaneous morphine, as needed every 4 hours to reduce breathlessness.	48 hours

RCT =randomized controlled trial



## Outcomes

### Patient- or Caregiver-Reported, or Observational Symptom-Related Outcomes

#### Breathlessness

Nine RCTs assessed the effects of respiratory interventions on breathlessness in patients with advanced cancer.<sup>20, 22-28</sup>

Three RCTs evaluated airflow in inpatient hospice or palliative care units.<sup>20-22</sup> All three assessed fan to face for 5 minutes, compared with either usual care<sup>21</sup> or sham intervention (fan to legs).<sup>20, 22</sup> All three RCTs assessed breathlessness using a 0-10 scale, using a numeric rating scale,<sup>21</sup> or an Edmonton Symptom Assessment System- Revised,<sup>20</sup> or the modified Borg Scale<sup>22</sup>. All three RCTs individually showed statistically significant and clinically meaningful improvement in breathlessness in the intervention arm compared with the control arm.<sup>20-22</sup> In the meta-analysis, the calculated standardized mean difference was -2.09 (95% confidence interval (CI), -3.81 to -0.37; I-squared, 94.3%) favoring the fan arm, which was both statistically significant and clinically meaningful (Figure 2).<sup>20, 21</sup> We concluded that fans were effective in improving breathlessness (SOE: Moderate).

Four RCTs evaluated compressed air compared with standard supplemental oxygen.<sup>23-26</sup> All RCTs included a crossover design but did not consistently report outcomes after the first and second intervention. Three RCTs assessed breathlessness using the visual analog scale (VAS) (0-100).<sup>24-26</sup> One RCT evaluated non-hypoxemic patients in an inpatient unit and reported that both groups had statistically significant improvement in breathlessness ( $p < 0.001$  for both arms), but there was no between group difference ( $p$  value not reported).<sup>24</sup> Effect size was not reported. In the subgroup of patients with hypoxemia, change in breathlessness score with standard supplemental oxygen had a weak correlation with baseline oxygen saturation (correlation coefficient, 0.13), although standard supplemental oxygen corrected hypoxemia in all patients.<sup>24</sup> One RCT evaluated hypoxemic patients (but required less than 4 L/minute of oxygen) and found a statistically significant and clinically meaningful improvement in breathlessness scores favoring oxygen, with a mean between group difference of 20.5 (95% CI, 13.5 to 27.6).<sup>26</sup> One RCT evaluated inpatients and outpatients and found no statistically significant difference in breathlessness between groups.<sup>25</sup> The calculated standardized mean difference was -0.23 (95% CI, -0.79 to 0.31). In the subgroup of patients with hypoxemia, there was also no statistically significant difference in breathlessness scores between groups, although standard supplemental oxygen corrected hypoxemia in 76% of patients. There was no significant correlation between breathlessness score and oxygen saturation (Spearman rank correlation coefficient, 0.019). This RCT also reported categorical data. The percentage of patients with subjective improvement was similar in both groups (calculated relative risk [RR], 0.80; 95% CI, 0.29 to 2.20). One RCT assessed breathlessness using a 0-10 numeric rating scale in non-hypoxemic patients and found no statistically significant difference in breathlessness between groups ( $p=0.52$ ).<sup>23</sup> Effect size was not reported. We concluded that compressed air and standard supplemental oxygen did not differ in improving breathlessness overall or in patients with or without baseline hypoxemia (SOE: Low).

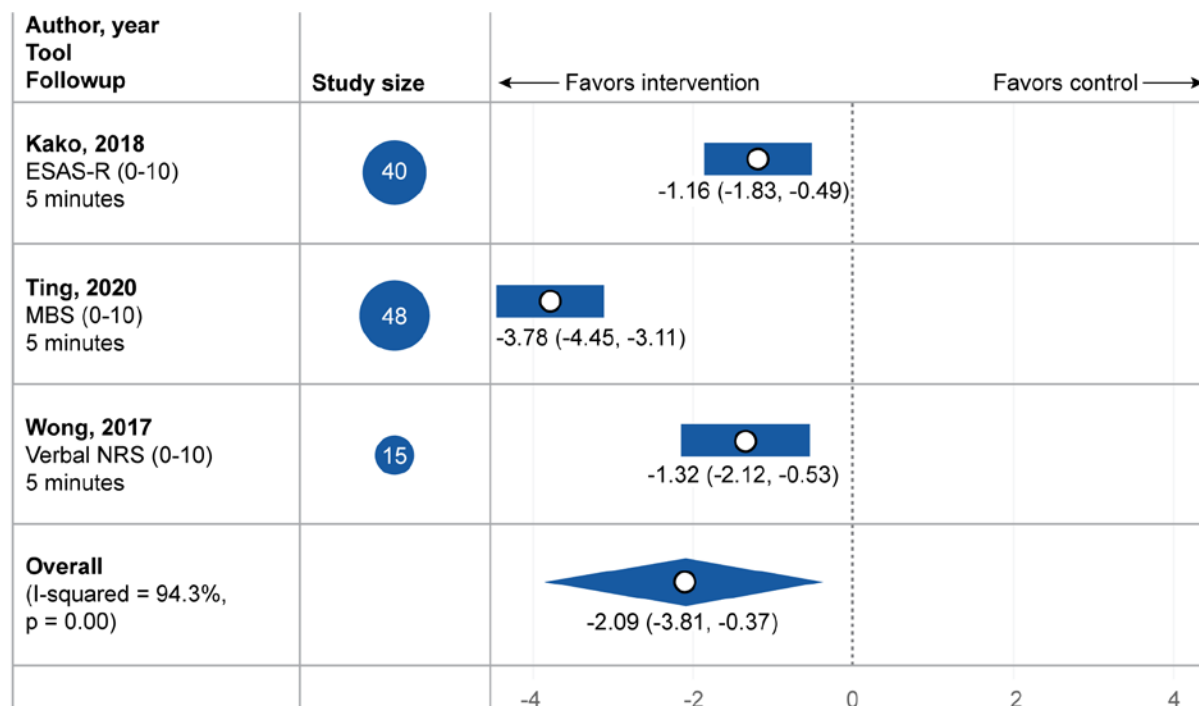
Two RCTs evaluated bilevel ventilation's effects on breathlessness in patients with advanced cancer.<sup>27, 28</sup> One RCT evaluated bilevel ventilation versus high flow nasal cannula (10-40 L/min)



in inpatients with baseline breathlessness despite use of standard supplemental oxygen.<sup>27</sup> The RCT reported statistically significant decrease in breathlessness 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 breathlessness was similar (calculated RR 0.85, 95% CI, 0.59 to 1.23). We concluded that bilevel ventilation and high flow nasal cannula did not differ in improving breathlessness (SOE: Low).

One RCT evaluated bilevel ventilation compared with standard supplemental oxygen in inpatients with baseline breathlessness and found a statistically significant improvement in breathlessness (Borg scale, 0-10) in the bilevel ventilation arm, compared with the standard supplemental oxygen arm ( $p=0.0012$ ).<sup>28</sup> 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 bilevel ventilation was effective for improving breathlessness compared with standard supplemental oxygen (SOE: Low).

**Figure 2. Meta-analysis of the effects of airflow on breathlessness in patients with advanced cancer in inpatient hospice or palliative care units compared with either usual care or sham intervention**



ESAS-R = Edmonton Symptom Assessment System- Revised scale; NRS = numerical rating scale, MBS = modified Borg scale, SMD – standardized mean difference  
 Circle size=corresponds to study size.  
 Length of the bar=corresponds to range of confidence interval.  
 Diamond=the result when all the individual studies are combined and averaged.



## **Anxiety**

One RCT (n=40) evaluated fan to face versus fan to legs and reported anxiety using the Edmonton Symptom Assessment System- Revised scale (0-10).<sup>20</sup> 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 standard supplemental oxygen reported functional status using a physical function subscale (range, 0-100).<sup>23</sup> The RCT found no statistically significant between group differences (p=0.64). Effect sizes were not reported.

## **Clinical or Utilization Health Outcomes**

### **Respiratory Rate**

Six RCTs reported on the effects of respiratory interventions on respiratory rate in patients with advanced cancer.<sup>20-22, 26-28</sup> For airflow interventions,<sup>20-22</sup> meta-analysis showed no statistically significant difference in respiratory rate between arms. The calculated standardized mean difference was -0.86 (95% CI: -2.33 to 0.60; I-squared, 79.1%). For bilevel ventilation,<sup>27, 28</sup> meta-analysis showed no statistically significant difference in respiratory rate between the bilevel ventilation arms and the control arms (high flow nasal cannula in one RCT, standard supplemental oxygen in one RCT)(Appendix C-Figure 2). The mean between-group difference was -0.754 (95% CI, -1.67 to 0.16; I-squared, 0.0%). In one RCT,<sup>26</sup> there was a statistically significant reduction in respiratory rate in the standard 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)**

Seven RCTs reported on the effects of respiratory interventions on oxygen, carbon dioxide or bicarbonate levels (oxygen saturation) in patients with advanced cancer.<sup>20-22, 25-28</sup> One RCT reported improvement in transcutaneous carbon dioxide in the high flow nasal cannula (10-40 L/min of oxygen) arm compared with the bilevel ventilation arm (p=0.02), but no between group differences in oxygen saturation (p=0.62).<sup>27</sup> Effect sizes were not reported. Another RCT evaluated bilevel ventilation compared with oxygen and showed a statistically significant difference in the partial pressure of oxygen (PaO<sub>2</sub>) (mean between group difference 5.17, 95% CI, 1.98 to 8.35) favoring the bilevel ventilation arm, but not in the partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>) (mean between group difference, -1.56; 95% CI, -3.13 to 0.02).<sup>28</sup>

For standard supplemental oxygen versus compressed air,<sup>25, 26</sup> one RCT reported no statistically significant difference in oxygen saturation between arms.<sup>26</sup> The calculated standardized mean difference was -0.98 (95% CI, -2.10 to 0.13).<sup>26</sup> Another RCT reported a statistically significant difference in oxygen saturation between groups, favoring the standard supplemental oxygen arm.<sup>25</sup> The mean absolute change in oxygen saturation (percentage) from baseline in the standard supplemental oxygen and compressed air arms was 5.43 percent and 0.94 percent respectively (between group p≤ 0.001).

For airflow interventions<sup>20-22</sup> 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 -0.37 (95% CI, -1.10 to 0.37; I-squared, 79.1%) (Appendix C-Figure 3).

## Heart Rate

Two bilevel ventilation RCTs<sup>27, 28</sup> and one airflow RCT reported on the effects on heart rate.<sup>20</sup> The meta-analysis of the bilevel ventilation RCTs showed a statistically significant between group difference in the decrease in heart rate, reduced more in the bilevel ventilation arm (mean between-group difference, -2.904; 95% CI, -5.47 to -0.336), (I-squared, 0.0%) (Appendix C-Figure 4).<sup>27, 28</sup> One RCT evaluated airflow and reported no statistically significant effect on heart rate (calculated standardized mean difference, -0.19; 95% CI, -0.82 to 0.42).<sup>20</sup>

## Blood Pressure

Two RCTs evaluated the use of bilevel ventilation in patients with advanced cancer and reported no statistically significant between group differences in the effects on blood pressure.<sup>27, 28</sup> The calculated standardized mean differences for systolic blood pressure was -0.62 (95% CI, -1.34 to 0.10) in one RCT<sup>27</sup>, and the mean between-group difference for blood pressure was -0.51 (95% CI, -21.13 to 1.12) in the other RCT.<sup>28</sup>

## Objective Measure of Exercise Capacity

One RCT (n=33) evaluated compressed air and standard supplemental oxygen and reported no statistically significant between groups differences in 6-minute walking distance (p=0.95).<sup>23</sup> Effect sizes were not reported. We were unable to draw conclusions (SOE: insufficient).

## Behavioral/Psychoeducational Interventions

### Description of Included Studies

Three RCTs (2 with some concerns and 1 with high risk of bias) evaluated behavioral/psychoeducational interventions in patients with advanced cancer. The control arm(s) were usual care in all three RCTs.<sup>29-31</sup> Table 5 provides an overview of included RCTs.

**Table 5. Overview of behavioral/psychoeducational interventions for patients with advanced cancer**

Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
Bordeleau, 2003 <sup>29</sup>  N=215	Multi-center, outpatient, North America  Breast cancer, Eastern Cooperative Oncology Group performance status 0-2, life expectancy >3 months  No funding source reported.	Usual care: Usual information regarding breast cancer, treatment, relaxation, nutrition  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)	4, 8, 12 months (primary follow up)



Author, Year Number of Patients	Study Characteristics	Intervention Description	Followup Duration
McMillan, 2007 <sup>31</sup>  N=328	Single-center, home hospice, North America  Primary cancer site not reported, Hospice patients with distress and identified caregiver  Government funding.	Usual care: General hospice care, routine education and support of caregivers as provided in hospice  Friendly visit group: Caregivers received general support without formal COPE (creativity, optimism, planning, and expert information) intervention. Three visits in 9 days.  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).	16 days and 30 days (primary follow up)
Moore, 2012 <sup>30</sup>  N=202	Multi-center, outpatient, Europe  Lung cancer and mesothelioma, 85% advanced, World Health Organization performance status 0-2, life expectancy > 3 months  Government funding	Usual care: Usual care.  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 at open access short notice appointments). Ensured rapid communication, regular contact and re-assurance, coordination of care. Regular discussion and referral for new or worsening symptoms.	3 months (primary follow up), 6 months and 12 months

## Outcomes

### Patient- or Caregiver-Reported, or Observational Symptom-Related Outcomes

#### Breathlessness

Three RCTs assessed the effects of behavioral or psychoeducational interventions on breathlessness in patients with advanced cancer.<sup>29-31</sup> One RCT assessed breathlessness using a breathlessness intensity scale (0-10).<sup>31</sup> 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 breathlessness ( $p=0.77$ ).<sup>31</sup> The random effect model estimate was -0.003 (standard error, 0.011). Two RCTs assessed breathlessness using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).<sup>29, 30</sup> 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).<sup>29</sup>

One RCT evaluated multidisciplinary nurse-led follow up versus usual care reported a statistically significant difference between groups in median breathlessness scores ( $p=0.03$ ), favoring the intervention arm)<sup>30</sup> 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/psychoeducational interventions did not consistently produce a clinically important improvement in breathlessness (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.<sup>29, 30</sup> 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).<sup>29</sup> One RCT evaluated multidisciplinary nurse-led follow up compared with usual care reported no statistically significant difference between groups (p 0.22).<sup>30</sup> 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/psychoeducational interventions on health-related quality of life in patients with advanced cancer.<sup>29-31</sup>

One RCT reporting 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).<sup>29</sup>

One RCT evaluating a problem-based coping intervention compared with usual care and friendly visits found no statistically significant differences in health-related quality of life between groups using the Hospice Quality-of-Life Index (p=0.246).<sup>31</sup> The random effect model estimate was 0.13 (standard error 0.11).

One RCT evaluated multidisciplinary nurse-led follow up compared with usual care reporting health-related quality of life using the EORTC core questionnaire reported no statistically significant difference between groups (p=0.82).<sup>30</sup> Effect sizes were not reported. We concluded that behavioral/psychoeducational interventions did not improve health-related quality of life (SOE: Low).

## **Clinical or Utilization Health Outcomes**

No RCTs of behavioral/psychoeducational interventions reported any clinical or health care utilization outcomes.

## **Activity/Rehabilitation Interventions**

### **Description of Included Studies**

Seven RCTs (4 with some concerns and 3 with high risk of bias) evaluated activity/rehabilitation interventions in patients with advanced cancer,<sup>36-42</sup> and two of the four included a crossover design.<sup>36, 41</sup> Two RCTs compared two different interventions,<sup>36, 38</sup> and five RCTs compared interventions with usual care.<sup>37, 39-42</sup> Table 6 provides an overview of the included RCTs.



**Table 6. Overview of activity/rehabilitation interventions for patients with advanced cancer**

	Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
<b>Exercise Therapy (1 RCT)</b>	Hwang, 2012 <sup>39</sup>  N=24	Single-center, outpatient, Asia  Lung cancer with EGFR mutation, age 40-75 years, Eastern Cooperative Oncology Group Performance Status 0-1  Funding source not reported	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	8 weeks
	Ligibel, 2016 <sup>40</sup>  N=101	Multi-center, outpatient, North America  Breast cancer (100%), life expectancy >1-year, Eastern Cooperative Oncology Group Performance Status 0-1, baseline <150 minutes of recreational activity per week  Non-profit funding.	Usual care: Usual care in clinic.  Exercise therapy: Goal was 150 minutes of moderate intensity exercise a week. In-person meetings x 4 weeks, then monthly until 16 weeks. Led by an exercise physiologist. Additional telephone contact and asked to practice at home. A heart rate monitor, pedometer, exercise journal, and local gym membership provided.	16 weeks
<b>Respiratory Training (1 RCT)</b>	Molassiotis, 2017 <sup>37</sup>  N=46	Multi-center, outpatient, Europe  Lung cancer/mesothelioma, 59% advanced cancer, with refractory breathlessness at rest or minimal exertion, life expectancy >3 months  Government funding	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.	12 weeks
<b>Exercise Therapy and Respiratory Training (3)</b>	Henke, 2014 <sup>38</sup>  N=29	Single-center, inpatient while receiving chemotherapy, Europe	Respiratory training and exercise therapy: Breathing techniques and conventional physiotherapy taught, including massage therapy if needed.	9 weeks (approximately )



	Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
<b>RCTs)</b>		Lung cancer, Karnofsky Performance Score >50%  Funding source not reported	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).	
	Vanderbyl, 2017 <sup>36</sup>  N=24	Single-center, outpatient, North America  Lung cancer (50%) and gastrointestinal cancers (50%), Eastern Cooperative Oncology Group Performance Status 0-2, life expectancy >4 months.  Non-profit funding	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 resistance training). Practice at home for 1 hour daily.  After 6 weeks, groups underwent crossover.	6 weeks, then crossover.
	Rutkowski, 2019 <sup>42</sup>  N=30	Single-center, inpatient, Europe  Lung cancer (100%), receiving inpatient chemotherapy, World Health Organization Performance Status 0-1, able to exercise.  Funding not reported	Usual care: Continued to receive usual inpatient care, including chemotherapy.  Exercise therapy and respiratory training: Five sessions/week, during weeks 2-3 of a 3-week chemotherapy cycle, for 2 chemotherapy cycles (total 4 weeks out of 6-week follow-up). Conducted by a certified physiotherapist. Approximately 2 hours per session. Each session had fitness (cycling or treadmill at 30-80% intensity of peak work rate), respiratory exercises (strengthening exercises for intercostal and diaphragm muscles, exhalation exercises, percussion therapy) for 30 minutes each and resistance exercises.	6 weeks
<b>Electrical Stimulation (1 RCT)</b>	Nakano, 2020 <sup>41</sup>  N= 20	Single-center, inpatient, Asia  Lung cancer/mesothelioma, 5%, patients with advanced cancer and cancer-associated pain receiving palliative care.	Usual care: Continued to receive usual inpatient palliative care, including opioids as clinically indicated.  Transcutaneous electrical nerve stimulation: Device had a 4-channel stimulator with four pairs of self-adhesive stimulating electrodes: one pair of on the back (pain), 2 pairs of gel pads on the back at the	6 days, then crossover.



	<b>Author, Year</b> <b>Number of Patients</b>	<b>Study Characteristics</b>	<b>Intervention Description</b>	<b>Followup Duration</b>
		Government and non-profit funding	C7 to Th8 dermatomal level (nausea, vomiting, and breathlessness), 1 pair behind the medial malleolus (constipation). High-frequency (100 Hz) stimulation used for all treatments except constipation (10 Hz). Intensity titrated until electrical sensation was strong but still comfortable. Delivered for 30-minutes daily, for 5 days, by a trained physical therapist.  After a 5-day washout, groups underwent crossover.	

RCT = randomized controlled trial; EGFR=epidermal growth factor receptor



## Outcomes

### Patient- or Caregiver-Reported or Observational Symptom-Related Outcomes

#### Breathlessness

Seven RCTs assessed the effects of activity/rehabilitation interventions on breathlessness in patients with advanced cancer.<sup>36-42</sup>

One RCT assessing breathlessness using a Likert scale (0-10) and evaluating exercise compared with Qigong (a mind-body exercise that combines meditation, slow physical movements and controlled breathing) reported no statistically significant difference between groups.<sup>36</sup> 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 breathlessness between groups after crossover ( $p=0.61$ , effect sizes not reported).<sup>36</sup>

One RCT evaluating inspiratory muscle training compared with usual care<sup>37</sup> reported breathlessness using the modified Borg scale (0-10) and found a statistically significant worsening in the usual care arm ( $p=0.03$ ) 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.

One RCT evaluated exercise therapy and respiratory training compared with usual care<sup>42</sup> using multiple scales. It reported no statistically significant effect on breathlessness on any scale: Modified Medical Research Council Dyspnea Scale (calculated standardized mean difference, 0.00; 95% CI, -0.76 to 0.76), Baseline Dyspnea Index (calculated standardized mean difference, 0.00; 95% CI, -0.76 to 0.76), and the Borg scale (calculated standardized mean difference, 0.09; 95% CI, -0.67 to 0.85).

Three RCTs evaluated breathlessness using the EORTC QLQ-C30 questionnaire.<sup>38-40</sup> One RCT evaluating exercise compared with usual care reported no statistically significant effect on breathlessness (calculated standardized mean difference, -0.35; 95% CI, -1.16 to 0.45).<sup>39</sup> One RCT evaluating a combination of exercise/respiratory training compared with conventional therapy<sup>38</sup> reported a statistically significant difference in breathlessness between arms, favoring the combination arm ( $p < 0.05$ ). Effect sizes were not reported. One RCT evaluated exercise compared with usual care and reported no statistically significant effect on breathlessness (calculated standardized mean difference, -0.48; 95% CI, -0.95 to -0.02).<sup>40</sup>

One RCT evaluated transcutaneous electrical nerve stimulation compared with usual care, in a crossover design, and reported breathlessness using the EORTC QLQ-C15-PAL instrument. This RCT reported no statistically significant difference between groups.<sup>41</sup> The calculated standardized mean difference was 0.07 (95% CI, -0.55 to 0.69).

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

#### Anxiety

Two RCTs assessed the effects of activity/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)<sup>36</sup> for the first comparison between interventions. The order of interventions did not have a statistically significant impact on anxiety ( $p=0.13$ ).

One RCT evaluating 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).<sup>37</sup> 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

Four RCTs evaluated the effects of activity/rehabilitation interventions on functional status using the EORTC QLQ-C30 or the EORTC QLQ-C15-PAL questionnaire (physical functioning).<sup>38-41</sup>

One RCT evaluating 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).<sup>39</sup>

One RCT evaluating a combination of exercise and respiratory training compared with conventional therapy<sup>38</sup> reported a statistically significant difference in function between arms, favoring the combination arm ( $p < 0.05$ ).

One RCT evaluated exercise compared with usual care and reported no statistically significant effect on functional status ( $p=0.25$ ). We could not calculate effect sizes.<sup>40</sup>

One RCT evaluated transcutaneous electrical nerve stimulation compared with usual care, in a crossover design, and reported functional status using the EORTC QLQ-C15-PAL instrument. This RCT reported no statistically significant difference between groups.<sup>41</sup> The calculated standardized mean difference was 0.54 (95% CI, -0.09 to 1.17). We could not calculate effect sizes or determine if this was clinically meaningful.

## Health-Related Quality of Life

Five RCTs reported on the effects of activity/rehabilitation interventions on health-related quality of life in patients with advanced cancer.<sup>36-39, 40</sup>

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)<sup>36</sup> for the first comparison between interventions. The trial found no statistically significant difference in health-related quality of life 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 ( $p=0.01$ ).<sup>36</sup>

One RCT evaluated inspiratory muscle training compared with usual care reported health-related quality of life using the Chronic Respiratory Disease Questionnaire.<sup>37</sup> 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.

Three RCTs reported on health-related quality of life using the EORTC QLQ-C30 questionnaire.<sup>38, 39, 40</sup> 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).<sup>39</sup> One RCT evaluated a combination of exercise and respiratory training compared with conventional physiotherapy and reported no statistically significant differences in health-related quality of life within or between groups ( $p > 0.05$ ).<sup>38</sup> We could not calculate effect sizes. One RCT evaluated exercise compared with usual care and reported no statistically significant effect on health-related quality of life (calculated standardized mean difference, 0.35; 95% CI, -0.11 to 0.81).<sup>40</sup>

We concluded that activity/rehabilitation interventions did not consistently improve health-related quality of life (SOE: Low).

## **Clinical or Utilization Health Outcomes**

### **Heart Rate**

One RCT ( $n=23$ ) evaluated exercise compared with usual care in patients with advanced cancer and reported no statistically significant effect on heart rate (calculated standardized mean difference, 0.16; 95% CI, -0.66 to 0.98).<sup>39</sup>

### **Blood Pressure**

One RCT ( $n=23$ ) evaluated exercise compared with usual care in patients with advanced cancer and reported no statistically significant effect on blood pressure (calculated standardized mean difference, 0.42; 95% CI, -0.43 to 1.29).<sup>39</sup>

### **Objective Measure of Exercise Capacity**

Three RCTs assessed the effects of activity/rehabilitation interventions on an objective measure of exercise capacity using the 6 Minute Walk Test.<sup>36, 38, 42</sup>

In one RCT evaluating exercise compared with Qigong, the calculated standardized mean difference was -1.4 (95% CI, -2.33 to -0.52), favoring the exercise arm.<sup>36</sup> 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.<sup>36</sup> 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 physiotherapy<sup>38</sup> and 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.

One RCT evaluated exercise therapy and respiratory training compared with usual care<sup>42</sup> and reported no statistically significant effect on the 6 Minute Walk Test (calculated standardized mean difference, 0.41; 95% CI, -0.36 to 1.17). We concluded that activity/rehabilitation interventions improved exercise capacity (SOE: Low).

## **Integrative Medicine Interventions**

### **Description of Included Studies**

Four RCTs (2 with some concerns and 2 with low risk of bias) evaluated integrative medicine interventions in patients with advanced cancer.<sup>32-35</sup> Three RCTs evaluated at least one



of three types of integrative medicine interventions: acupuncture, acupressure, or reflexology.<sup>32-</sup>  
<sup>34</sup> One RCT evaluated music therapy.<sup>35</sup> Table 7 provides an overview of included RCTs.



**Table 7. Overview of integrative medicine interventions for patients with advanced cancer**

	Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
<b>Acupressure (1 RCT)</b>	Dogan, 2019 <sup>34</sup>  N=60	Single-center, outpatient, Asia  Lung cancer, 97% advanced, life expectancy >3 months, baseline $\geq$ 3/10 breathlessness on modified Borg scale  Funding source not reported.	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.	4 weeks
<b>Acupuncture and Acupressure (1 RCT)</b>	Vickers, <sup>32</sup>  N=45	Single-center, inpatient and outpatient, North America  Lung (80%) or breast (20%) cancer, baseline breathlessness (American Thoracic Society Breathlessness score 2 or higher)  Government funding.	Placebo: Sham acupuncture needles (blunted needles) applied in body areas away from breathlessness sites, for 15 minutes, by Licensed acupuncturists. Then, sham acupressure studs 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 <i>de qi</i> , 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	15 minutes, and 1 week
<b>Reflexology (1 RCT)</b>	Wyatt, 2012 <sup>33</sup>  N=286	Multi-center, outpatient, North America  Breast cancer, able to perform basic activities of daily living, no specific baseline breathlessness score.  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)



	<b>Author, Year</b>	<b>Study Characteristics</b>	<b>Intervention Description</b>	<b>Followup Duration</b>
<b>Music Therapy (1 RCT)</b>	Ramirez, 2018 <sup>35</sup>  N=40	Single-center, inpatient palliative care unit, Europe  Primary cancer site not reported, terminally ill patients, no specific baseline breathlessness score.  Government and non-profit funding.	Control group: 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



## Outcomes

### Patient- or Caregiver-Reported or Observational Symptom-Related Outcomes

#### Breathlessness

Four RCTs assessed the effects of integrative medicine interventions on breathlessness in patients with advanced cancer.<sup>32, 33, 35</sup>

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 breathlessness with reflexology.<sup>33</sup> 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 and reported no statistically significant difference in breathlessness (using a 0-10 breathlessness 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.<sup>32</sup>

One RCT evaluating acupressure assessed breathlessness using the modified Borg scale (0-10) and reported a statistically significant between group difference in median breathlessness 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.<sup>34</sup> We could not determine if this was clinically meaningful. We concluded that acupressure/reflexology were more effective at reducing breathlessness than usual care or sham procedures (SOE: Low).

One RCT evaluated music therapy and reported statistically significant improvement in breathlessness scores (Edmonton Symptom Assessment System, 0-10) in the music therapy group ( $p=0.042$ ) but not in the control group. Between group differences and effect sizes were not reported.<sup>35</sup> 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 integrative medicine on anxiety in advanced cancer patients.<sup>33, 35</sup>

One RCT reported the State-Trait Anxiety Inventory for anxiety.<sup>33</sup> 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 (Edmonton Symptom Assessment System [ESAS], 0-10) in the music therapy group ( $p=0.002$ ) but not in the control group. Between group differences and effect sizes were not reported.<sup>35</sup> 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).<sup>33</sup> The mean improvement in physical functioning for the reflexology group compared with usual care group was statistically significant (p=0.04). The adjusted effect sizes for reflexology versus usual care were estimated to be 0.21 at week 5 and 0.44 at week 11. We could not determine if this was clinically meaningful. We could not draw a conclusion about reflexology.

## **Health-Related Quality of Life**

Two RCTs reported on the effects of integrative medicine on health-related quality of life in patients with advanced cancer.<sup>33, 34</sup>

One RCT reported health-related quality of life using the St George's Respiratory Questionnaire (0-100),<sup>34</sup> and the other reported health-related quality of life using the Functional Assessment of Cancer Therapy–Breast (FACT-B), version 4 questionnaire (0-180).<sup>33</sup> Meta-analysis of these two RCTs showed no statistically significant difference in health-related quality of life between arms. The meta-analysis should be interpreted with caution given the substantial heterogeneity. The calculated standardized mean difference was -2.00 (95% CI, - 5.76 to 1.76), (I-squared = 98.5%) (Appendix C-Figure 6). We concluded that acupressure/reflexology did not improve 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.<sup>34</sup> Acupressure significantly improved respiratory rate (p≤ 0.001) and 6 minute walking distances (p=0.046) but not oxygen saturation or heart rate, compared with usual care. We could not calculate effect sizes. We were unable to draw conclusions about exercise capacity (SOE: Insufficient) or other clinical or utilization health outcomes.

## **Multicomponent Interventions**

### **Combined Activity/Rehabilitation and Behavioral/Psychoeducational Interventions**

#### **Description of Included Studies**

Three RCTs evaluated a combination of activity/rehabilitation and behavioral/psychoeducational interventions in patients with advanced cancer.<sup>43-45</sup> Two RCTs had high risk of bias<sup>43, 44</sup>, and one RCT had some concerns.<sup>45</sup> Table 8 provides an overview of included RCTs.



**Table 8. Overview of activity/rehabilitation and behavioral psychoeducational interventions for patients with advanced cancer**

Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
Corner, 1996 <sup>44</sup>  N=20	Single-center, outpatient, Europe  Lung cancer  Non-profit funding	Control: Usual care (Allowed to talk freely about breathlessness but no specific counseling/retraining)  Intervention: Respiratory training (breathing re-training) and behavioral therapy (counseling, relaxation, coping) sessions, once weekly in a nurse-led clinic.	4 weeks and 12 weeks (primary follow up).
Chan, 2011 <sup>43</sup>  N=140	Single-center, outpatient, Asia  Lung cancer, Karnofsky Performance Scale >60%, receiving palliative radiation.  Government funding.	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.	3, 6 and 12 weeks (primary follow up).
Dhillon, 2017 <sup>45</sup>  N=111	Multi-center, outpatient, Australia  Lung cancer, Eastern Cooperative Oncology Group Performance Status 0-2, life expectancy > 6 months, medically fit to exercise.  Government and non-profit funding.	Control: Usual care, including educational materials on cancer-specific exercise and nutrition.  Intervention: Eight sessions, held weekly, each lasting 1 hour (45 minutes exercise, 15 minutes behavioral support) with a trainer. Goal was to increase recreational activity by >3 metabolic equivalent of task (MET) hours/week, individualized to baseline fitness and interests. Home exercise encouraged. All participants received a pedometer, activity diary, and workbook. Also, behavior change program based on Theory of Planned Behavior, including goal setting/planning, social support, stimulus control and decision balance.	2 months (primary follow up), 4 and 6 months

## Outcomes

### Patient- or Caregiver-Reported or Observational Symptom-Related Outcomes

#### Breathlessness

Three RCTs assessed breathlessness.<sup>43-45</sup> Two RCTs assessed breathlessness using the VAS (0-10).<sup>43, 44</sup> One RCT reported within group median improvements in breathlessness scores of -0.5 (range, -5.7 to 1) in usual care, and 0.5 (range, -0.5 to 2.8) in intervention arms.<sup>44</sup> 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 breathlessness at 6 weeks ( $p = 0.002$ , partial eta-squared 0.04) and 12 weeks ( $p = 0.001$ , partial eta-squared 0.043).<sup>43</sup> These indicate small effect sizes. We could not determine if this was clinically meaningful.



One RCT evaluated breathlessness using the San Diego Shortness of Breath Questionnaire <sup>45</sup> and reported no statistically significant between group differences in breathlessness at 2 months ( $p=0.28$ ). We could not calculate effect sizes. We concluded that combination activity/rehabilitation and behavioral/psychoeducational interventions did not consistently improve breathlessness compared with usual care (SOE: Low).

## **Anxiety**

Three RCTs assessed anxiety.<sup>43-45</sup> 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 the intervention arm.<sup>44</sup> 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).<sup>43</sup> These indicate small effect sizes. We could not determine if this was clinically meaningful.

One RCT evaluated anxiety using the General Health Questionnaire-12 <sup>45</sup> reported no statistically significant between group differences in anxiety at 2 months ( $p=0.52$ ). We could not calculate effect sizes. We concluded that a combination of activity/rehabilitation and behavioral/psychoeducational interventions did not consistently improve anxiety compared with usual care (SOE: Low).

## **Functional Status**

Three RCTs assessed functional status.<sup>43-45</sup> One RCT reported difficulties in performing activities of daily living (as reported on the Exercise 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.<sup>44</sup> 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).<sup>43</sup> We could not determine if this was clinically meaningful.

One RCT evaluated functional status using the EORTC QLQ-C30 <sup>45</sup> and reported no statistically significant between group differences in functional status at 2 months ( $p=0.81$ ). We could not calculate effect sizes.

## **Health-Related Quality of Life**

One RCT assessed health-related quality of life using the EORTC QLQ-C30 <sup>45</sup> and reported no statistically significant between group differences in health-related quality of life at 2 months ( $p=0.82$ ). We could not calculate effect sizes. We were unable to draw conclusions about health-related quality of life (SOE: Insufficient).



## Clinical or Utilization Health Outcomes

### Objective Measure of Exercise Capacity

One RCT assessed the effects of a combination of activity/rehabilitation and behavioral/psychoeducational interventions on an objective measure of exercise capacity using the 6 Minute Walk Test.<sup>45</sup> and reported no statistically significant between group differences in exercise capacity of life at 2 months ( $p=0.97$ ) or 6 months ( $p=0.89$ ). We could not calculate effect sizes. We were unable to draw conclusions about exercise capacity (SOE: Insufficient).

## Combined Activity/Rehabilitation, Behavioral/Psychoeducational, and Integrative Medicine

### Description of Included Studies

Two RCTs with high risk of bias evaluated a combination of activity/rehabilitation, behavioral/psychoeducational, and integrative medicine interventions.<sup>46, 47</sup> One of them had a crossover design (i.e., delayed intervention), where the control group received the intervention after two weeks.<sup>46</sup> However, no outcomes after crossover were presented. Table 9 provides an overview of included RCTs.

**Table 9. Overview of activity/rehabilitation, behavioral/psychoeducational, and integrative medicine interventions for patients with advanced cancer**

Author, Year  Number of Patients	Study Characteristics	Intervention Description	Followup Duration
Yorke, 2015 <sup>47</sup>  N=101	Multi-center, primarily outpatient, Europe  Lung cancer, 59% advanced, World Health Organization Performance Status 0-2, patients 'bothered' by at least 2 of the 3: breathlessness, cough, or fatigue.  Non-profit funding	Control: usual care  Intervention: Respiratory training (breathing re-training and cough easing techniques), behavioral therapy (counselling, caregiver support, acceptance, locus control), and acupuncture.	4 weeks and 12 weeks (primary followup).
Farquhar, 2014 <sup>46</sup>  N=67	Single-center, outpatient, Europe  Lung cancer/mesothelioma (54%), patients referred to breathlessness service (exact baseline breathlessness scores not reported)  Government and non-profit funding	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.	2 weeks; data for crossover not presented separately.



## **Outcomes**

### **Patient- or Caregiver-Reported, or Observational Symptom-Related Outcomes**

#### **Breathlessness**

Two RCTs assessed breathlessness using the Numeric Rating Scale (0 to 10).<sup>46, 47</sup> In one RCT, the mean between group difference was not statistically significant, 0.65 (95% CI, -0.49 to 1.80)<sup>47</sup>. This RCT also reported the Breathlessness-12 scale (range, 0 to 36).<sup>47</sup> 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.<sup>46</sup> We concluded that multicomponent activity/rehabilitation, behavioral psychoeducational, and integrative medicine interventions were more effective at improving breathlessness than usual care (SOE: Low).

#### **Anxiety**

Two RCTs assessed anxiety using the Hospital Anxiety and Depression Scale<sup>46, 47</sup>. Meta-analysis showed 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%) (Appendix C-Figure 5). We concluded that multicomponent activity/rehabilitation, behavioral psychoeducational, and integrative medicine interventions were not effective at improving anxiety compared with 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<sup>47</sup> and Chronic Respiratory Questionnaire (CRQ)-7 at 2 weeks.<sup>46</sup> 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%). We concluded that multicomponent activity/rehabilitation, behavioral psychoeducational, and integrative 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.<sup>46</sup>

## **Behavioral, Psychoeducational, and Integrative Medicine**

### **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.<sup>48</sup> 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 breathlessness and Patient-Reported Outcomes Measurement Information System for anxiety at two and six weeks.

### **Outcomes**

#### **Patient- or Caregiver-Reported, or Observational Symptom-Related Outcomes**

##### **Breathlessness**

One RCT (n=50) reported no statistically significant effect on breathlessness (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/psychoeducational and integrative medicine interventions reported any clinical or utilization health outcomes.



**Key Question 2. What are the comparative benefits of pharmacological interventions (either alone or in combination) for improving breathlessness in patients with advanced cancer?**

## **Key Points**

- Opioids were not more effective than placebo for improving breathlessness in patients with advanced cancer within the limits of the identified studies (SOE: Moderate). In addition, there was no difference in effectiveness between doses or routes of opioids (SOE: Low).
- Anxiolytics were not more effective than placebo for improving breathlessness or anxiety in patients with advanced cancer (SOE: Low).
- Opioids were not more effective than anxiolytics for improving breathlessness in patients with advanced cancer (SOE: Low).
- We were unable to draw conclusions for corticosteroids or comparisons between other pharmacological interventions for improving breathlessness or anxiety in patients with advanced cancer (SOE: Insufficient).
- Opioids were not more effective than placebo for improving exercise 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).

## **Description of Included Studies**










We identified 18 studies ( 17 RCTs and 1 retrospective study) including 1,224 patients assessing the benefits of medications for the management of breathlessness in advanced cancer.<sup>49-66</sup> Eighteen studies assessed eight different medications over eight different routes of administration. Nine RCTs were placebo-controlled, and eight RCTs and one retrospective study assessed comparisons between drugs. Six RCTs evaluated treatments for exertional breathlessness while four RCTs and one retrospective study evaluated chronic breathlessness. Five RCTs did not report the type of breathlessness evaluated, and two reported on acute breathlessness. Followup ranged from one minute to 28 days. Five RCTs were multicenter.<sup>50, 53, 59, 61, 65</sup> Four RCTs were industry-funded, all of which assessed fentanyl in various routes of administration (buccal, intranasal, and sublingual).<sup>49, 51, 53, 64</sup> Six RCTs and one retrospective study were supported by government funding<sup>49-52, 61, 63, 64</sup> and 11 RCTs were supported by non-profit organizations.<sup>49, 51, 52, 54, 56-58, 60, 64-66</sup> Two RCTs did not report a funding source<sup>59, 62</sup> and one reported no funding.<sup>55</sup>

The characteristics of the studies, participants, and interventions are listed in Appendix D-Evidence Tables D-2, D-5, D-9, D-10 and D-14. See Appendix D Evidence Tables D-40 through D-49 for details of the outcome data. The summary of key findings and strength of evidence are presented in Tables 10 and 11.







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






**Table 10. Summary of key results for the effects of pharmacological interventions on breathlessness in patients with advanced cancer**

Comparison Category Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
<b>Placebo-controlled comparisons</b>  <b>Opioids vs. placebo</b>	 Equivalence	 Moderate	 6 RCTs <sup>49, 51, 54, 55, 60, 62</sup> N = 107  Fentanyl vs. placebo (4) Hydromorphone (nebulized) vs. hydromorphone (Oral or subcutaneous) vs. placebo (nebulized) (1) Morphine vs placebo (1)	Pooled analysis with Charles, 2008 <sup>60</sup> saline vs. nebulized hydromorphone comparison: • SMD: -0.12 (95% CI: -0.45 to 0.2), • I-squared=0.0%  Pooled analysis with Charles, 2008 <sup>60</sup> saline vs. systemic hydromorphone comparison: • SMD: -0.14 (95% CI: -0.47 to 0.18) • I-squared=0.0%	Opioids were not more effective than placebo within the limits of the identified studies.
<b>Placebo-controlled comparisons</b>  <b>Anxiolytics vs. placebo</b>	 Equivalence	 Low	 2 RCTs <sup>50, 65</sup> N= 311  Buspirone vs. placebo (1) Midazolam vs. placebo (1)	Buspirone vs. Placebo: • Reported MBGD: -0.52; 95% CI: -1.045 to 0.005  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.	Anxiolytics were no more effective than placebo
<b>Placebo-controlled comparisons</b>  <b>Corticosteroids vs. placebo</b>	 No conclusion drawn	 Insufficient	 1 RCT <sup>52</sup> N = 28  Dexamethasone vs. placebo (1)	Calculated SMD: -0.06; 95% CI: -0.7 to 0.58	Not applicable



Comparison Category Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
<b>Drug-drug comparisons</b>  <b>Opioid vs. opioid</b>	 Equivalence	 Low	 7 RCTs <sup>53, 56, 59-61, 64, 66</sup> N = 132  Subcutaneous vs. sublingual morphine (1) Subcutaneous vs. nebulized morphine (1) High vs. low dose sublingual fentanyl (1) Low vs. high dose opioids (drug unspecified) (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or subcutaneous) vs. placebo (nebulized) (1) Buccal fentanyl vs. oral morphine (1) Oral morphine hydrochloride vs. oral morphine sulfate (1)	Pooled analysis: <ul style="list-style-type: none"> <li>SMD: 0.15 (95% CI: -0.22 to 0.52)</li> <li>I-squared=4.8%</li> </ul>	There was no difference in effectiveness between opioid doses or routes in improving breathlessness
<b>Drug-drug comparisons</b>  <b>Opioids vs. anxiolytics</b>	 Equivalence	 Low	 2 RCTs <sup>57, 58</sup> N = 108  Oral morphine vs. oral midazolam (1) Subcutaneous morphine vs. subcutaneous midazolam vs. combination (1)	For breathlessness intensity: <ul style="list-style-type: none"> <li>One study found midazolam was more effective than morphine at 5 days (<math>p &lt; 0.001</math>)</li> <li>Second study found no significant differences between groups at 24 h or 48 h</li> </ul> For categorical variable of percent not experiencing breathlessness relief: <ul style="list-style-type: none"> <li>Calculated RR: 0.075; 95% CI, 0.004 to 1.27</li> <li>Calculated RR: 1.33; 95% CI, 1.02 to 1.75</li> </ul>	Opioids were not more effective than anxiolytics for improving breathlessness









Comparison Category Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed†	Key Findings	Conclusion
<b>Drug-drug comparisons</b>  <b>Opioid vs. corticosteroids vs. bronchodilators</b>	 No conclusion drawn	 Insufficient	 1 retrospective cohort <sup>63</sup> N = 343  Morphine vs. methylprednisolone vs. aminophylline (1)	Methylprednisolone vs. aminophylline: <ul style="list-style-type: none"> <li>Calculated SMD, 0.41; 95% CI, 0.15 to 0.68</li> </ul> Morphine vs. aminophylline, <ul style="list-style-type: none"> <li>Calculated SMD, 1.18; 95% CI, 0.9 to 1.46</li> </ul> Morphine vs. methylprednisolone, <ul style="list-style-type: none"> <li>Calculated SMD, 0.76; 95% CI: 0.49 to 1.03</li> </ul>	Not applicable

CI: confidence intervals; SMD: standardized mean difference; RCT: randomized controlled trial; RR: relative risk; MBGD: mean between group difference; vs= versus;




\*Moderate strength indicates that further research may change the result; low strength indicates low confidence that the evidence reflects the true effect, and further research is very likely to change the result, and insufficient evidence indicates that evidence is unavailable or does not permit a conclusion.

†The diameter of each circle is linearly related to the number of patients in trials of that comparison/outcome.

**Table 11. Summary of key results for the effects of pharmacological interventions on anxiety, health-related quality of life, and exercise capacity in patients with advanced cancer**

Comparison Category Outcome Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed	Key Findings	Conclusion
<b>Placebo-controlled comparisons</b>  <b>Anxiety</b>  <b>Anxiolytics vs. Placebo</b>	 Equivalence	 Low	 2 RCTs <sup>50, 65</sup> N= 311  Buspirone vs. placebo (1)  Intranasal midazolam vs. placebo	Buspirone vs. placebo <ul style="list-style-type: none"> <li>No statistically significant differences between groups; unable to calculate SMD.</li> </ul> Intranasal midazolam vs. placebo <ul style="list-style-type: none"> <li>No difference between arms reported by authors</li> </ul>	Anxiolytics were not more effective than placebo for improving anxiety
<b>Placebo-controlled comparisons</b>  <b>Health related quality of life</b>  <b>Corticosteroids vs. Placebo</b>	 No conclusion drawn	 Insufficient	 1 RCT <sup>52</sup> N = 28 oral dexamethasone vs. placebo	Calculated SMD, -0.06; 95% CI, -0.7 to 0.58	Not applicable



Comparison Category Outcome Comparison	Evidence of Difference	Strength of Evidence*	Number of Studies and N Analyzed	Key Findings	Conclusion
Placebo-controlled comparisons  Exercise capacity  Opioid vs. placebo	 Equivalence	 Moderate	 4 RCTs <sup>49, 51, 54, 55</sup> N = 77  Fentanyl vs. placebo	Pooled analysis of 3 studies: <ul style="list-style-type: none"> <li>• SMD, 0.063; 95% CI, -0.43 to 0.55</li> <li>• I-squared=0.0%</li> </ul> Fourth study reported no significant differences between groups. Unable to calculate SMD, data reported as medium, rather than mean average.	Opioids were not more effective than placebo for improving exercise capacity

SMD: standardized mean difference; RR: relative risk; MBGD: mean between group difference; vs= versus; NA=not applicable

\*Moderate strength indicates that further research may change the result; low strength indicates low confidence that the evidence reflects the true effect, and further research is very likely to change the result, and insufficient evidence indicates that evidence is unavailable or does not permit a conclusion.

\*The diameter of each circle is linearly related to the number of patients in trials of that comparison/outcome.

## Outcomes

### Patient- or Caregiver-Reported, or Observational Symptom-Related Outcomes

#### Breathlessness

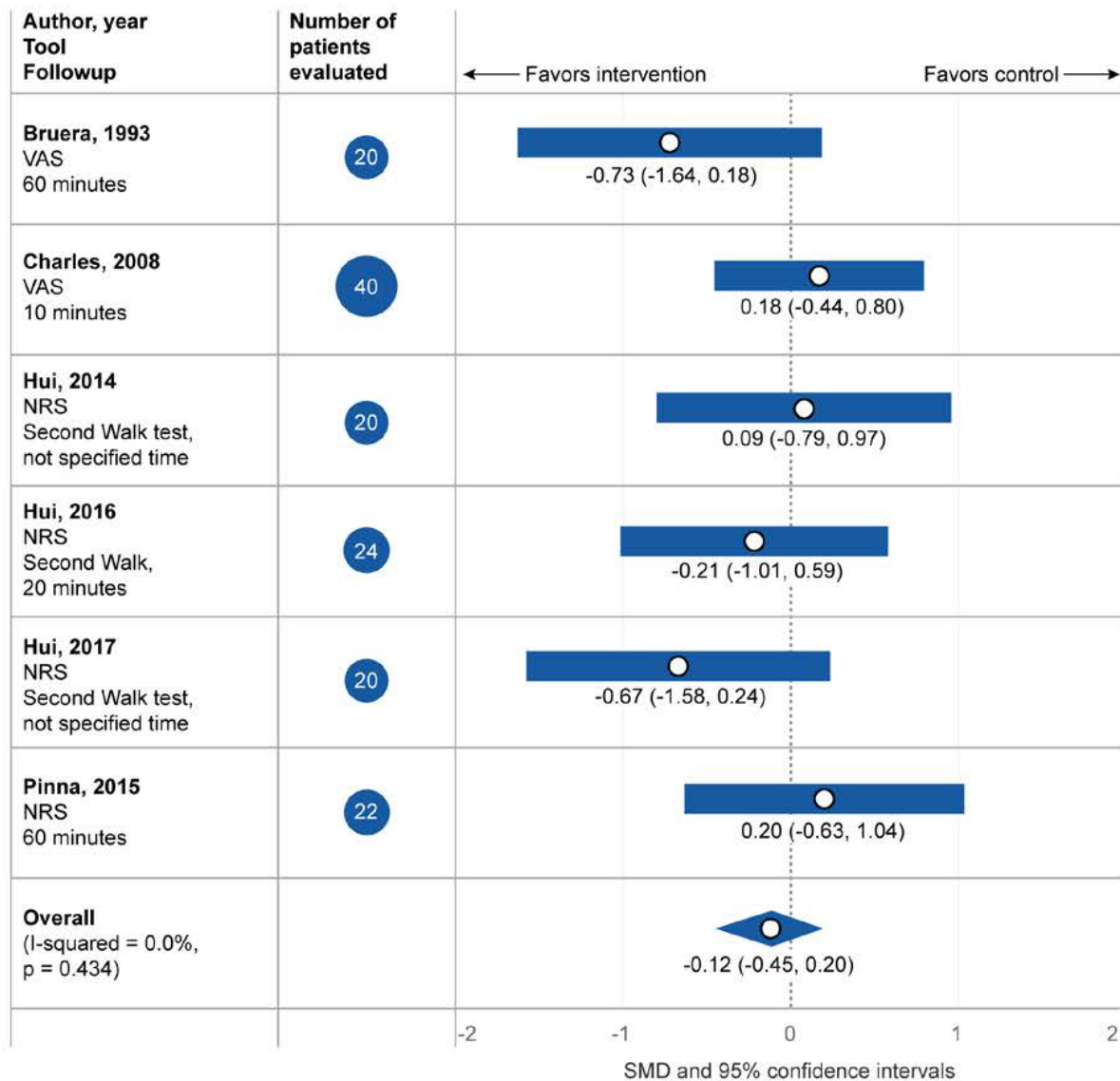
#### Placebo-Controlled Comparisons

##### Opioids Versus Placebo

Six RCTs (3 with low, 1 with some concerns, and 2 with high risk of bias) assessed the effect of opioids compared with placebo on breathlessness.<sup>49, 51, 54, 55, 60, 62</sup> Four RCTs compared fentanyl products (intranasal, buccal, transmucosal and subcutaneous) to placebo for the treatment of exertional breathlessness.<sup>49, 51, 54, 55</sup> One RCT evaluated hydromorphone (nebulized or subcutaneous) compared with nebulized saline in acute breathlessness.<sup>60</sup> and one RCT evaluated subcutaneous morphine compared with placebo, although the type of breathlessness was undefined. Two meta-analyses are reported here to reflect the two placebo comparisons provided in one of the RCTs<sup>60</sup> (calculated standardized mean difference with Charles, 2008 et al.<sup>60</sup> saline versus nebulized hydromorphone comparison, -0.12; 95% CI, -0.45 to 0.20, I-squared=0.0%) (calculated standardized mean difference with Charles, 2008 et al.<sup>60</sup> saline versus systemic hydromorphone comparison, -0.14; 95% CI, -0.47 to 0.18, I-squared=0.0%)(Figures 3 and 4). Based on the overall pooled results from the meta-analysis, opioids were not more effective than placebo for improving breathlessness in advanced cancer patients (SOE: Moderate).



**Figure 3. Meta-analysis of the effects on breathlessness in randomized controlled trials comparing opioids with placebo in patients with advanced cancer (including Charles, 2008,<sup>60</sup> saline versus nebulized hydromorphone comparison)**



*Figure 1*

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

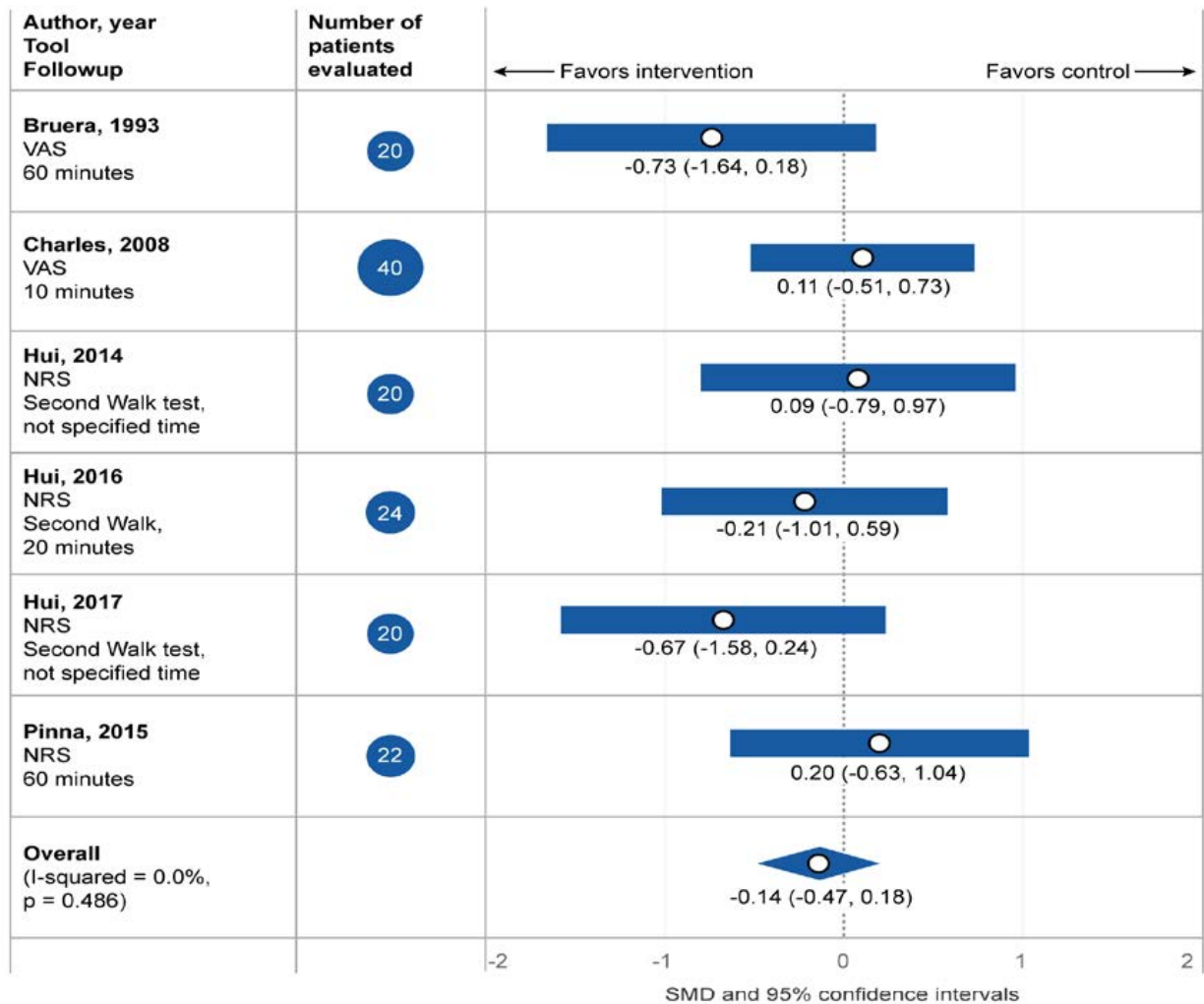
Circle size=corresponds to study size.

Length of the bar=corresponds to range of confidence interval.

Diamond=the result when all the individual studies are combined and averaged.



**Figure 4. Meta-analysis of the effects on breathlessness in randomized controlled trials comparing opioids with placebo in patients with advanced cancer (including Charles, 2008,<sup>60</sup> saline versus systemic hydromorphone comparison)**



VAS=visual analog scale; NRS= numerical rating scale; SMD =standardized mean difference  
 Circle size=corresponds to study size; Length of the bar=corresponds to range of confidence interval.  
 Diamond=the result when all the individual studies are combined 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 breathlessness in patients with advanced cancer.<sup>50, 65</sup>

One RCT compared oral buspirone with placebo to treat chronic breathlessness. Breathlessness was assessed after 28 days using the Oxygen Cost Diagram, a VAS scale assessing tolerance for exertion with scores ranging from 2 to 14.<sup>50</sup> The study found no statistically significant difference between groups (reported mean between-group difference, -0.52; 95% CI, -1.045 to 0.005), which was also likely not clinically significant



Another RCT evaluated intranasal midazolam versus placebo over 60 minutes and found no statistically significant difference in breathlessness between groups ( $p=0.75$ ).<sup>65</sup> 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 breathlessness (SOE: Low).

## **Corticosteroids Versus Placebo**

One RCT with low risk of bias compared oral dexamethasone with placebo and assessed chronic breathlessness at 7 days in patients with advanced cancer.<sup>52</sup> This RCT reported no statistically significant effect for corticosteroids compared with placebo in breathlessness (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 with placebo for the treatment of breathlessness in advanced cancer (SOE: Insufficient).

## **Drug-Drug Comparisons**

### **Opioids Versus Opioids**

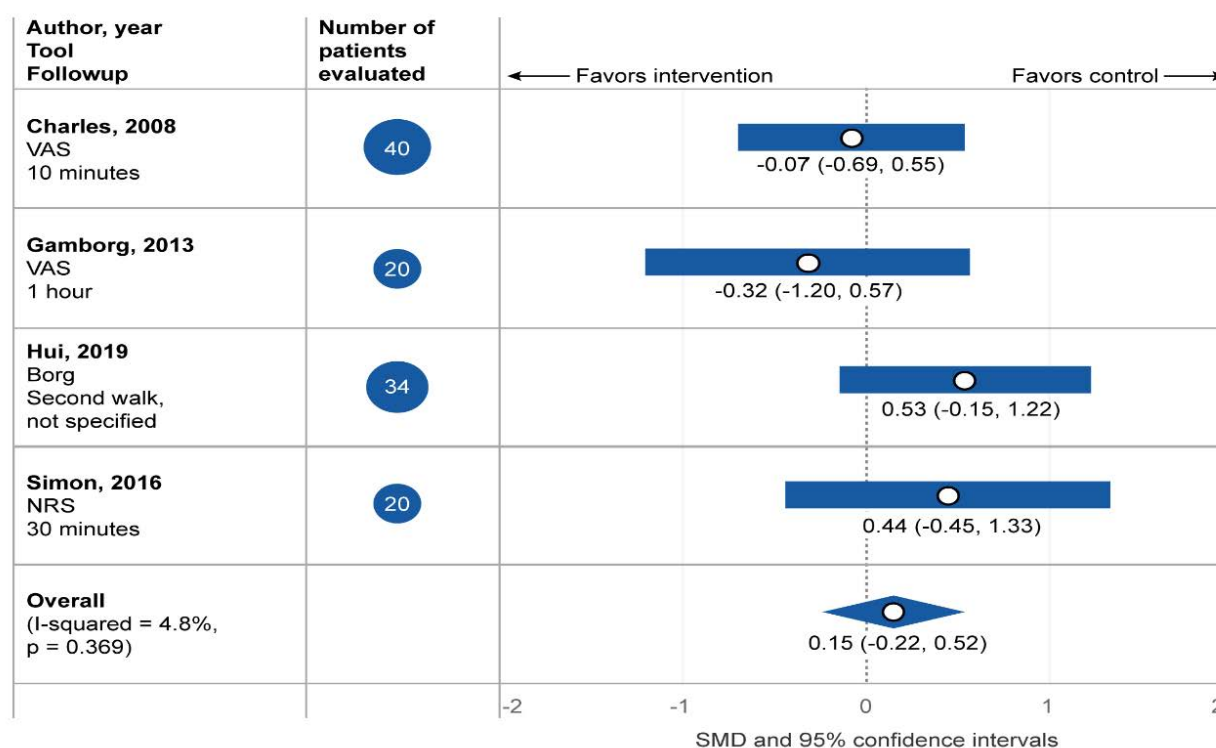
Seven RCTs (2 with low, 1 with some concerns, and 4 with high risk of bias), compared the effect of either different routes of administration or different doses of opioids for the treatment of breathlessness in patients with advanced cancer.<sup>53, 56, 59-61, 64, 66</sup> Two RCTs evaluated exertional breathlessness, two evaluated chronic breathlessness, one evaluated acute breathlessness and two did not specify a breathlessness type.

Two RCTs compared different routes of morphine administration (subcutaneous versus sublingual morphine, and subcutaneous versus nebulized morphine)<sup>56, 59</sup> while a third RCT compared two different formulations of oral morphine (morphine hydrochloride versus morphine sulfate).<sup>66</sup> A fourth RCT compared different routes of hydromorphone administration (nebulized versus systemic).<sup>60</sup> while a fifth RCT compared buccal fentanyl to oral morphine.<sup>53</sup> Two other RCTs compared different doses of opioid (high dose versus low dose fentanyl, and low dose versus high dose opioids).<sup>61, 64</sup> 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). 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 four RCTs,<sup>53, 56, 60, 64</sup> no difference was seen between opioid doses or routes in treating breathlessness in advanced cancer patients (calculated standardized mean difference, 0.15; 95% CI, -0.22 to 0.52, I-squared=4.8%) (Figure 5) (SOE: Low).

Three RCTs could not be included in the analysis as they reported results as median, rather than mean, data were derived from figures or not enough information was included for calculations.<sup>59, 61, 66</sup> One RCT evaluated subcutaneous versus nebulized morphine and reported no statistically significant differences between groups at 60 minutes. Another RCT evaluated high dose versus low dose opioids and reported no significant differences between groups. The third RCT evaluated different formulations of oral morphine for exertional breathlessness and reported a significant difference favoring morphine hydrochloride at 1 minute and 3 minutes post administration which did not persist over 5 minutes.



**Figure 5. Meta-analysis of the effects on breathlessness in randomized controlled trials comparing opioids with opioids in patients with advanced cancer**



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

In “Number of Patients Evaluated” column, circle size around each number corresponds to study size.

In third column, the length of the horizontal bar corresponds to the range of the confidence interval.

In fifth line, the diamond represents the result when all the individual studies are combined 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.<sup>57, 58</sup> In one RCT of oral morphine compared with oral midazolam, midazolam was more effective at relieving breathlessness at 5 days ( $p < 0.001$ ).<sup>57</sup> 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 breathlessness 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<sup>58</sup>. The study found no statistically significant differences in breathlessness 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 breathlessness 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 breathlessness 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 breathlessness (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.<sup>63</sup> 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 breathlessness 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 breathlessness 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.<sup>50</sup> The study reported no statistically significant differences between groups (reported mean between-group difference, 1.83; 95% CI, -0.092 to 3.746), which was likely also not clinically significant. 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.<sup>65</sup> 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 breathlessness (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.<sup>52</sup> Although specific data were 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**

The summary of findings for the effects of pharmacological interventions on clinical utilization health outcomes is presented in the Appendix C (Table 1).

## **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.<sup>49, 51</sup> Both RCTs were of exertional breathlessness 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-squared=31.6%) and (Systolic, calculated standardized mean difference, 0.478; 95% CI, -0.13 to 1.09, I-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.<sup>64</sup> 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.<sup>49, 51, 60</sup> Two RCTs compared fentanyl to placebo for exertional breathlessness, and the third compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline for acute breathlessness. Based on the pooled results of the meta-analysis, we found no significant difference between opioids and placebo in the effect on heart rate. We report two meta-analyses to reflect the two placebo comparisons provided in one of the RCTs<sup>60</sup> (calculated standardized mean difference with Charles, 2008 et al.<sup>60</sup> saline versus nebulized hydromorphone comparison, -0.14; 95% CI, -0.57 to 0.29, I-squared=0.0%) (calculated standardized mean difference with Charles, 2008 et al.<sup>60</sup> saline versus systemic hydromorphone comparison, -0.03; 95% CI, -0.46 to 0.4, I-squared=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.<sup>56, 60, 64</sup> One RCT<sup>64</sup> evaluated high doses versus low doses of fentanyl sublingual spray for exertional breathlessness, the second RCT evaluated the effect of oral versus subcutaneous morphine on breathlessness at rest.<sup>56</sup> and the third compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline for acute breathlessness<sup>60</sup>. 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**

Six RCTs (1 with some concerns, 3 with low , and 2 with high risk of bias) compared opioids with placebo in patients with advanced cancer and reported on oxygen saturation.<sup>49, 51, 54, 55, 60, 62</sup> Four RCTs compared fentanyl with placebo in the treatment of exertional breathlessness. One RCT compared morphine with placebo in the treatment of unspecified breathlessness. One RCT compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline in the treatment of acute breathlessness.

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<sup>60</sup> (calculated standardized mean difference with Charles, 2008 et al.<sup>60</sup> saline versus nebulized hydromorphone comparison, -0.07; 95% CI, -0.40 to 0.25, I-squared=0.0%) (calculated standardized mean difference with Charles,



2008 et al.<sup>60</sup> saline versus systemic hydromorphone comparison, -0.13; 95% CI, -0.45 to 0.19, I-squared=0.0%) (Appendix C-Figures 11 and 12).

## **Drug-Drug Comparisons**

### **Opioids Versus Opioids**

Three RCTs (1 with low and 2 with high risk of bias) compared opioids and reported oxygen saturation for patients with advanced cancer.<sup>53, 60, 64</sup> One RCT compared high dose versus low dose fentanyl spray for exertional breathlessness. One RCT compared oral morphine vs oral fentanyl for acute breathlessness. The third RCT compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline in the treatment of acute breathlessness.

Based on the pooled results of the meta-analysis, we found no difference in the effect on oxygen saturation (calculated standardized mean difference, 0.03; 95% CI, -0.44 to 0.37, 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.<sup>57, 58</sup> One RCT randomized patients to receive either oral morphine or oral midazolam.<sup>57</sup> 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 breathlessness were randomized to three groups. Group M<sub>0</sub> received around the clock morphine with rescue midazolam, group M<sub>1</sub> 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**

Five RCTs (3 with low and 2 with high risk of bias) reported effects of opioids compared with placebo on respiratory rate in patients with advanced cancer.<sup>49, 51, 54, 60, 62</sup> Three RCTs compared fentanyl with placebo in the treatment of exertional breathlessness. One RCT compared morphine with placebo in the treatment of unspecified breathlessness. The fifth study compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline in the treatment of acute breathlessness.

Based on the overall pooled results of six 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<sup>60</sup> (calculated standardized mean difference with saline versus nebulized hydromorphone comparison, 0.11; 95% CI, -0.25 to 0.47, I-squared=0.00%) (calculated standardized mean difference with saline versus systemic



hydromorphone comparison, 0.05; 95% CI, -0.31 to 0.41, I-squared=1.0%) (Appendix C-Figures 14 and 15).

## **Drug-Drug Comparisons**

### **Opioids Versus Opioids**

Four RCTs (1 with some concerns, 1 with low, and 2 with high risk of bias) reported effects of different opioid regimens on respiratory rate in patients with advanced cancer.<sup>53, 60, 61, 64</sup> 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 oral morphine with oral fentanyl. One RCT compared high dose versus low dose fentanyl spray for exertional breathlessness and the fourth RCT compared nebulized hydromorphone versus systemic hydromorphone versus nebulized saline in the treatment of acute breathlessness.

Based on the overall pooled results of four RCTs, we found no difference between opioids in the effect on respiratory rate (calculated standardized mean difference, -0.23; 95% CI, -0.63 to 0.18, I-squared=0.0%) (Appendix C-Figure 16). One RCT<sup>61</sup> 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 showed a statistically significant within-group reduction in mean respiratory frequency after administration of the supplementary dose.

## **Objective Measure of Exercise Capacity**

### **Placebo-Controlled Comparisons**

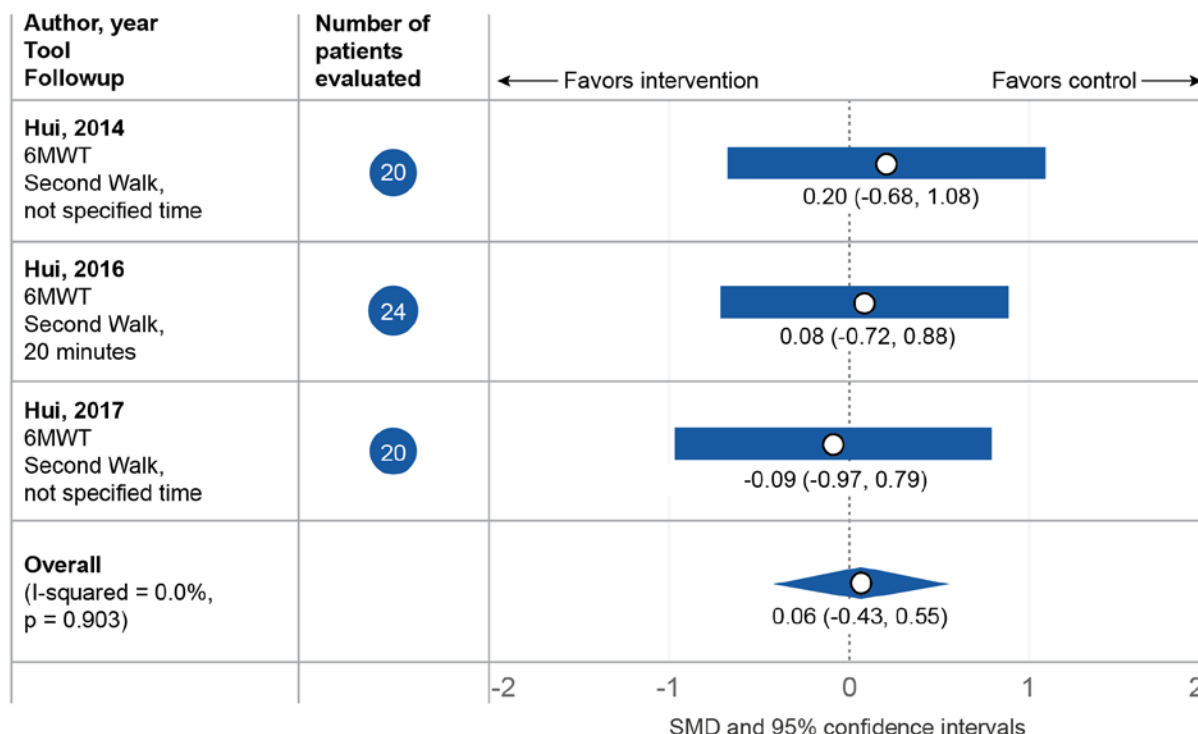
#### **Opioids Versus Placebo**

Four RCTs (1 with some concerns and 3 with low risk of bias) reported outcomes in terms of distance in a six-minute walk test.<sup>49, 51, 54, 55</sup> All four RCTs compared fentanyl with placebo for the treatment of exertional breathlessness. In a pooled analysis of three RCTs<sup>51, 54</sup>, we found no differences in six-minute walk distance for opioids compared with placebo (calculated standardized mean difference, 0.06; 95% CI, -0.43 to 0.55, 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.<sup>55</sup> 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.<sup>55</sup> 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 exercise capacity (SOE: Moderate).



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



6MWT=6-minute walk test; SMD=standardized mean difference

In “Number of Patients Evaluated” column, circle size around each number corresponds to study size.

In third column, the length of the horizontal bar corresponds to the range of the confidence interval.

The diamond represents the result when all the individual studies are combined and averaged.

## Drug-Drug Comparisons

No drug versus drug comparisons reported on exercise capacity.

**Key Question 3.** What are the comparative benefits of nonpharmacological, pharmacological, and multimodal interventions for improving breathlessness in patients with advanced cancer?

## Key Point

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

## Description of Included Studies

Two RCTs (287 patients) addressed the benefits of nonpharmacological, pharmacological and multimodal interventions for managing breathlessness in patients with advanced cancer. One single center RCT (some concerns in at least one risk of bias tool domain, enrolled 173 patients)<sup>67</sup> randomized participants to acupuncture alone (integrative medicine), morphine alone (opioids), or a combination of both. Second single center RCT (some concerns in at least one risk



of bias tool domain)<sup>68</sup> enrolled 114 patients with lung cancer or head and neck cancer. Patients were randomized to usual care or a 24-week intervention addressing treatment of chronic obstructive pulmonary disease, including physician visits, medication changes, and education. The study was conducted in the outpatient setting with a primary followup of 25 weeks. The characteristics of the study, participants, and interventions are listed in Appendix D-Evidence Tables D-3, D-6, D-11, D-12 and D-15. See Appendix D Evidence Tables D-73 through D-79 for details of the outcome data. The summary of key findings and strength of evidence are presented in Table 12.

## **Outcomes**

### **Patient- or Caregiver-Reported, or Observational Symptom-Related Outcomes**

#### **Breathlessness**

In the RCT of acupuncture and morphine, there was no statistically significant difference in breathlessness 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).<sup>67</sup> Because of the concern for study limitations and the imprecise results, we were unable to draw conclusions from this single study (SOE: Insufficient). In the RCT evaluating multimodal management of chronic obstructive pulmonary disease versus usual care, there was no significant difference in breathlessness scores between arms, for either the EORTC QLQ (calculated standardized mean difference, -0.08; 95% CI, -0.53 to 0.36) or its 13-item lung cancer-specific questionnaire (calculated standardized mean difference, 0.01; 95% CI, -0.45 to 0.31).<sup>68</sup> Because of the concern for study limitations and the imprecise results, we were unable to draw conclusions from this single study (SOE: Insufficient).<sup>68</sup>

#### **Anxiety**

In the study of acupuncture and morphine, there were no statistically 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 conclusions from this single study (SOE: Insufficient).



## Functional Status

In the RCT evaluating multimodal management of chronic obstructive pulmonary disease versus usual care, there was no statistically significant difference in functional status between arms for the EORTC QLQ (calculated standardized mean difference, -0.14; 95% CI, -0.59 to 0.31). Because of the concern for study limitations and the imprecise results, we were unable to draw conclusions from this single study (SOE: Insufficient).<sup>68</sup>

## Health-Related Quality of Life

The RCT evaluating acupuncture, morphine, and the combination of both measured health-related quality of life 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 conclusions from this single study (SOE: Insufficient).

In the RCT evaluating multimodal management of chronic obstructive pulmonary disease versus usual care, there was no statistically significant difference in health-related quality of life between arms for the EORTC QLQ tool (calculated standardized mean difference, 0.21; 95% CI, -0.25 to 0.66). Because of the concern for study limitations and the imprecise results, we were unable to draw conclusions from this single study (SOE: Insufficient).<sup>68</sup>

## Clinical or Utilization Health Outcomes

The RCT did not evaluate any of these outcomes.

**Table 12. Summary of key results for the effects of nonpharmacological, pharmacological, and multimodal interventions on breathlessness, anxiety, and health-related quality of life in patients with advanced cancer**

Comparison	Outcome	Number of Studies Reporting Outcome (N Analyzed)	Findings	Strength of Evidence
Opioids vs. acupuncture vs. combination <sup>67</sup>	Breathlessness	1 RCT (145)	No significant differences between groups	Insufficient
	Anxiety	1 RCT (145)	We were unable to draw any conclusions	Insufficient
	Health-related quality of life	1 RCT (145)	No significant differences at the final time point between	Insufficient
Multimodal management of chronic obstructive pulmonary disease <sup>68</sup>	Breathlessness	1 RCT (77)	No significant differences between groups	Insufficient
	Health-related quality of life	1 RCT (74)	No significant differences between groups	Insufficient

RCT =randomized controlled trial



**Key Question 4. What are the harms of nonpharmacological and pharmacological interventions for improving breathlessness in patients with advanced cancer?**

## **Key Points**

### **Nonpharmacological Interventions**

- Bilevel ventilation was associated with equipment discomfort/distress in some participants, leading to dropouts in some participants.
- Activity/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.

## **Nonpharmacological Interventions**

### **Description of Included Studies**

Five RCTs addressed physical harms associated with nonpharmacological interventions in patients with advanced cancer.<sup>27, 28, 34, 37, 45</sup> Two RCTs evaluated bilevel ventilation<sup>27, 28</sup> with followup of 2 hours to 48 hours. One RCT each assessed activity/rehabilitation (12-week followup)<sup>37</sup>, multicomponent interventions incorporating activity/rehabilitation (6-month followup)<sup>45</sup>, and acupressure (4-week followup).<sup>34</sup> The characteristics of the studies, populations, and interventions are listed in Appendix D-Evidence Tables D-1, D-4, D-7, D-8 and D-13.



## Patient-Centered Adverse Effects of Breathlessness 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 D-28 to D-39.

### Respiratory Interventions

Two RCTs evaluating bilevel ventilation in an inpatient setting for patients with advanced cancer reported equipment discomfort/distress, insomnia, and gastrointestinal harms.<sup>27, 28</sup>

One RCT evaluated bilevel ventilation compared with high flow nasal cannula for 2 hours.<sup>27</sup> 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 nasal cannula arm (on a 0-10 scale, median change in oxygen arm, -6; median change in bilevel ventilation 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).

Bilevel ventilation was compared with standard supplemental oxygen for 48 hours in another RCT<sup>28</sup>. The study found no statistically significant differences in adverse events between arms. The calculated RR (standard supplemental oxygen arm compared with the bilevel ventilation 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/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.<sup>37</sup> The rate of discomfort/distress (fatigue, chest muscle soreness) (calculated RR, 24 (95% CI: 1.50 to 383.26) were more common in the intervention arm. The rate of central nervous system symptoms (attributed to hypercapnia) (calculated RR, 8.64 (95% CI: 0.49 to 152.01) were similar between arms. None of these led to dropouts.

### Multicomponent Interventions

One RCT evaluated exercise training and behavioral therapy compared with usual care in patients with advanced cancer for 8 weeks, with planned followup of 6 months, and reported equipment discomfort/distress.<sup>45</sup> The rate of discomfort/distress (back or muscle soreness) (calculated RR, 8.84 (95% CI: 0.49 to 160.44) was not statistically different between arms. None of these led to dropouts.

### Integrative Medicine Interventions

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).<sup>34</sup>



## **Dropouts**

The rates of dropout and details are presented in Appendix C (Table 2). The range of dropouts was 23 to 33 percent for activity/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 integrative 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 3). 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 D-2, D-5, D-9, D-10 and D-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 D-50 to D-72. The dropout results are summarized in Table 13.

## **Patient-Centered Adverse Effects of Breathlessness Treatments**

### **Central Nervous System (Cognitive Changes, Dizziness, Drowsiness, Fatigue, Headache, Respiratory Depression)**

#### **Placebo-Controlled Comparisons**

##### **Opioids Versus Placebo**

Three RCTs<sup>49, 51, 54</sup> 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 breathlessness, with comparisons after a second walk test).

One RCT<sup>51</sup> reported on cognitive changes with neurocognitive testing and found no significant changes in either the fentanyl or placebo arms.

Two RCTs<sup>49, 51</sup> 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%) (Appendix C-Figure 17).

All three RCTs reported on drowsiness. One RCT<sup>51</sup> had a calculated RR for drowsiness of 0.5 (95% CI: 0.05 to 4.81) and one RCT<sup>49</sup> 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%) (Appendix C-Figure 18).

One RCT<sup>54</sup> 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%) (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<sup>65</sup> 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 breathlessness<sup>52</sup> reported drowsiness and fatigue. The study found a significantly higher mean change (less drowsy) 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<sup>59, 64, 69</sup> (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 breathlessness 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)<sup>64</sup> Another RCT<sup>69</sup> reported cognitive changes only overall (not by study arm).

One RCT<sup>64</sup> 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<sup>59</sup> reported drowsiness (as sedation) as median only, so a standardized mean difference could not be calculated. One RCT<sup>69</sup> reported drowsiness only overall (not by study arm).

One RCT<sup>64</sup> 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).<sup>64</sup>

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 breathlessness in patients with advanced cancer reported on cognitive changes (cognitive disturbance) and drowsiness (somnolence).<sup>57</sup> 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 breathlessness in patients with advanced cancer reported cognitive changes (hallucinations), and dizziness and drowsiness (reported as somnolence)<sup>58</sup>. 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 breathlessness in patients with advanced cancer reported on dizziness and drowsiness (as somnolence).<sup>63</sup> 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<sup>49, 51, 54, 55</sup> reported gastrointestinal adverse effects for opioids (all fentanyl) compared with placebo in patients with advanced cancer (one for diarrhea<sup>55</sup> and three for nausea<sup>49, 51, 54</sup>).

One RCT<sup>55</sup> reported on diarrhea, but RR could not be calculated [2 (18%) events in both groups].

An RCT<sup>49</sup> 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<sup>54</sup> 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<sup>51</sup> 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.<sup>52</sup> For diarrhea, one (7.1%) event was reported in the dexamethasone group versus none in the placebo group (calculated 3.2 95% CI: 0.14 to 72.62).<sup>52</sup> 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).<sup>52</sup>



## Drug-Drug Comparisons

### Opioids Versus Opioids

Three studies reported on nausea in patients with advanced cancer receiving opioids to reduce breathlessness.<sup>59, 64, 69</sup> One RCT of high dose versus low dose fentanyl<sup>64</sup> reported no significant difference between groups (p value not significant) and one RCT of subcutaneous versus nebulized morphine<sup>59</sup> reported no significant difference (p=0.32) (mean differences not reported for either study). One retrospective cohort of oxycodone versus hydrocodone<sup>69</sup> reported only overall events.

### Opioids Versus Anxiolytics

One RCT of midazolam versus morphine<sup>57</sup> 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.<sup>57</sup> For moderate nausea, the calculated RR was 0.32 (95% CI, 0.01 to 7.65) for midazolam compared with morphine (p not significant).<sup>57</sup>

### Opioids Versus Corticosteroids Versus Bronchodilators

One retrospective cohort reported on constipation for morphine compared with methylprednisolone or aminophylline in patients with advanced cancer.<sup>63</sup> 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<sup>58</sup> 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<sup>49, 54</sup> of fentanyl compared with placebo in patients with advanced cancer reported on pruritus. One RCT<sup>49</sup> 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<sup>54</sup> did not report values for change but had no significant between-group difference (p=0.15).

## Drug-Drug Comparisons

### Opioids Versus Opioids

Two RCTs<sup>64, 69</sup> comparing opioids with opioids in patients with advanced cancer reported on pruritus as an adverse event. One RCT of high versus low dose fentanyl<sup>64</sup> 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<sup>69</sup> 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).<sup>57</sup>

## **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.<sup>69</sup>

#### **Opioids Versus Anxiolytics**

One RCT compared morphine versus midazolam for breathlessness 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).<sup>57</sup>

#### **Opioids Versus Anxiolytics Versus Combination**

One RCT<sup>58</sup> compared morphine versus midazolam with morphine and midazolam together reported on dry mouth.<sup>58</sup> 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<sup>63</sup> 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.<sup>49, 50, 52, 57, 60</sup> The rates are listed in Table 13.



**Table 13. Rate of dropouts due to adverse effects of pharmacological interventions for breathlessness in patients with advanced cancer**

<b>Drug Class</b>	<b>Intervention</b>	<b>Dropouts Due to Adverse Effects, n (%)</b>
<b>Opioids</b>	Fentanyl <sup>49</sup>	1 (9.1%)
	Hydromorphone <sup>60</sup>	4 (16%)
	Morphine <sup>57</sup>	1 (3.2%)
<b>Anxiolytics</b>	Midazolam <sup>57</sup>	1 (3.2%)
	Buspirone <sup>50</sup>	10 (4.7%)
<b>Corticosteroids</b>	Dexamethasone <sup>52</sup>	1 (5.6%) – 1 (7.1%)

## **Nonpharmacological Compared With Pharmacological Interventions**

One RCT (173 patients) compared opioids versus acupuncture versus a combination of both in patients with advanced cancer.<sup>67</sup> 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. Details of the adverse events reported in the study can be found in Appendix D-Evidence Tables D-80 to D-82.



## Discussion

### Findings in Relation to the Decisional Dilemma(s)

We identified 50 studies that assessed the benefits and harms of nonpharmacological and pharmacological treatments for breathlessness in advanced cancer. The review examined nonpharmacological interventions (including respiratory, behavioral/psychoeducational, activity/rehabilitation, integrative 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 breathlessness. Airflow interventions (fans) were more effective than sham or usual care for improving breathlessness, based on two studies in the inpatient setting (strength of evidence [SOE]: Moderate). Non-invasive positive pressure ventilation was more effective than supplemental oxygen for improving breathlessness (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/psychoeducational interventions alone nor activity/rehabilitation interventions alone were more effective than usual care for improving breathlessness or health-related quality of life, although activity/rehabilitation interventions did improve exercise capacity (SOE: Low) (Table 14 and Appendix C-Table 4).

Acupressure/reflexology were more effective than usual care or sham at improving breathlessness (SOE: Low). In addition, multicomponent interventions were more effective than usual care for improving breathlessness when they combined behavioral/psychoeducational interventions, activity/rehabilitation interventions and integrative medicine interventions (SOE: Low).

Opioids were not effective for the outcomes of breathlessness or exercise capacity, within the limits of the identified studies mainly focusing on exertional breathlessness (SOE: Moderate). We found no differences in effectiveness between different doses or routes of administration of opioids for improving breathlessness (SOE: Low). Anxiolytics were not more effective than placebo for improving breathlessness, and opioids were not more effective than anxiolytics for improving breathlessness (SOE: low). Evidence for the outcomes of anxiety, health-related quality of life and exercise 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 nonpharmacological and pharmacological interventions.

Regarding harms, noninvasive positive pressure ventilation was associated with equipment discomfort/distress in some participants, leading to dropouts in some. Few nonpharmacological 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 pharmacological 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.<sup>70</sup> Longitudinal data in patients with advanced



cancer showed that opioids and anxiolytics may have long-term adverse effects on functional status and cognitive and gastrointestinal symptoms.<sup>71</sup> A systematic review of adverse effects of corticosteroids in advanced cancer<sup>72</sup> 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 pharmacological interventions have extensive labeling on adverse events and many, particularly opioids and anxiolytics, also have Food and Drug Administration black box warnings. For nonpharmacological 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 both pharmacological and nonpharmacological interventions, particularly opioids<sup>73, 74</sup> we found stronger evidence to support nonpharmacological as opposed to pharmacological interventions. Evidence in broader populations with advanced chronic disease also supports various nonpharmacological treatments, including relaxation, reducing room temperature and humidifying air, and, elevating the head of the bed.<sup>9, 10</sup> A meta-analysis on oxygen compared with air<sup>75</sup> for mildly or non-hypoxemic patients with chronic obstructive pulmonary disease did show evidence for effectiveness with a small effect size. For pharmacological interventions, we did not find evidence to support the effectiveness of opioids within the limits of the identified studies focusing on exertional breathlessness. In contrast to our analysis, a meta-analysis of broader populations with a variety of advanced illnesses found evidence for the effectiveness of opioids with a small effect size, although evidence for cancer patients (which did not include many of the studies in our review) and chronic obstructive pulmonary disease (COPD) was insufficient.<sup>76</sup> In this broader meta-analysis, evidence was also of low quality, followup was generally only 1-2 days, and few patients were already on chronic opioids.<sup>76</sup> The previous meta-analysis found that the evidence for opioids for improving exercise capacity was conflicting<sup>76</sup> and that nebulized opioids were not more effective than nebulized saline.<sup>76</sup> A recent large trial of specific opioid approaches in mixed populations with chronic breathlessness also did not show a benefit for opioids.<sup>77, 78</sup> Evidence in broader populations also does not support effectiveness in reducing breathlessness for nebulized diuretics<sup>79</sup> or anxiolytics.<sup>80, 81</sup>



**Table 14. Summary of the strength of evidence for the key outcomes**

<b>Intervention category</b>	<b>Interventions</b>	<b>Breathlessness: Number of Studies (N Analyzed)</b>	<b>Anxiety: Number of Studies (N Analyzed)</b>	<b>Exercise Capacity: Number of Studies (N Analyzed)</b>	<b>Health-Related Quality of Life: Number of Studies (N Analyzed)</b>
<b>Nonpharmacological interventions</b>	Airflow vs. usual care or sham control	<ul style="list-style-type: none"> <li>• 3 RCTs (115)</li> <li>• Mod. evidence</li> <li>• Improvement</li> </ul>	<ul style="list-style-type: none"> <li>• 1 RCT (40)</li> <li>• Insuff. evidence</li> </ul>	NR	NR
	Compressed air vs. standard supplemental oxygen	<ul style="list-style-type: none"> <li>• 4 RCTs (96)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>	NR	<ul style="list-style-type: none"> <li>• 1 RCT (33)</li> <li>• Insuff. evidence</li> </ul>	NR
	Bilevel ventilation vs. high flow nasal cannula	<ul style="list-style-type: none"> <li>• 1 RCT (30)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>	NR	NR	NR
	Bilevel ventilation vs. standard supplemental oxygen	<ul style="list-style-type: none"> <li>• 1 RCT (189)</li> <li>• Low evidence</li> <li>• Improvement</li> </ul>	NR	NR	NR
	Behavioral/psycho educational interventions vs. usual care	<ul style="list-style-type: none"> <li>• 3 RCTs (197)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>	NR	NR	<ul style="list-style-type: none"> <li>• 3 RCTs (197)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>
	Acupuncture vs. sham acupuncture	1 RCT (33) Insuff. evidence	NR	NR	NR
	Acupressure/reflexology vs. sham intervention or usual care or both	<ul style="list-style-type: none"> <li>• 2 RCTs (206)</li> <li>• Low evidence</li> <li>• Improvement</li> </ul>	1 RCT (222) Insuff. evidence	1 RCT (60) Insuff. evidence	<ul style="list-style-type: none"> <li>• 2 RCTs (206)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>
	Music therapy vs. control group	1 RCT (40) Insuff. evidence	1 RCT (40) Insuff. evidence	NR	NR
	Activity/rehabilitation interventions vs. activity/rehabilitation interventions or usual care	<ul style="list-style-type: none"> <li>• 7 RCTs (227)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>	2 RCTs (60) Insuff. evidence	<ul style="list-style-type: none"> <li>• 3 RCTs (72)</li> <li>• Low evidence</li> <li>• Improvement</li> </ul>	<ul style="list-style-type: none"> <li>• 5 RCTs (188)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>
	Multicomponent combined behavioral/psycho educational and activity/rehabilitation interventions, vs. usual care	<ul style="list-style-type: none"> <li>• 3 RCTs (184)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>	<ul style="list-style-type: none"> <li>• 3 RCTs (212)</li> <li>• Low evidence</li> <li>• Equivalence</li> </ul>	1 RCT (62) Insuff. evidence	1 RCT (62) Insuff. evidence



Intervention category	Interventions	Breathlessness: Number of Studies (N Analyzed)	Anxiety: Number of Studies (N Analyzed)	Exercise Capacity: Number of Studies (N Analyzed)	Health-Related Quality of Life: Number of Studies (N Analyzed)
	Multicomponent combined behavioral/psycho educational, activity/rehabilitation and integrative medicine interventions, vs. usual care	2 RCTs (100) • Low evidence • Improvement	2 RCTs (99) • Low evidence • Equivalence	NR	2 RCTs (99) • Low evidence • Equivalence
	Multicomponent combined behavioral/psycho educational and integrative medicine interventions vs. usual care	1 RCT (38) Insuff. evidence	1 RCT (38) Insuff. evidence		NR
<b>Pharmacological interventions</b>	Opioids vs. placebo	6 RCTs (107) • Mod. Evidence • Equivalence	NR	4 RCTs (77) • Mod. Evidence • Equivalence	NR
	Anxiolytics vs. placebo	2 RCTs (311) • Low evidence • Equivalence		NR	NR
	Corticosteroids vs. placebo	1 RCT (28) Insuff. evidence	NR	NR	1 RCT (28) Insuff. evidence
	Opioid vs. opioid	7 RCTs (132) • Low evidence • Equivalence	NR	NR	NR
	Opioids vs. anxiolytics	2 RCTs (108) • Low evidence • Equivalence	NR	NR	NR
	Opioid vs. corticosteroids vs. bronchodilators	1 Retrospective cohort (343) Insuff. evidence	NR	NR	NR
<b>Nonpharmacological, pharmacological, and multimodal interventions</b>	Opioid vs. acupuncture vs. opioid-acupuncture combinations	1 RCT (145) Insuff. evidence	1 RCT (145) Insuff. evidence	NR	1 RCT (145) Insuff. evidence
	Multimodal management of chronic obstructive pulmonary disease	1 RCT (77) Insuff. evidence	NR	NR	1 RCT (74) Insuff. evidence

Insuff=insufficient; Mod=moderate; N=sample size; NR=not reported; RCT=randomized controlled trial



## Strengths and Limitations

The evidence for breathlessness in advanced cancer included studies of a wide variety of interventions, types of breathlessness, and settings. However, studies were generally small and often pilot trials or with low recruitment rates and with only short-term followup of minutes to a few weeks. We did not include articles with an initial sample size of less than 10 patients, and one opioid study with only nine patients was therefore not included, although given the small sample, inclusion would have not changed the conclusions.<sup>82</sup> Some studies for opioids were also conducted more than three decades ago, at a time when treatments for cancer and complications were much more limited. Outcome assessments were limited, mostly addressing breathlessness through a unidimensional visual analog scale (VAS) rather than recommended multidimensional comprehensive tools.<sup>4</sup> Baseline levels of breathlessness varied and interventions may not have primarily targeted breathlessness, and many studies found strong placebo effects. Few studies addressed other key outcomes of anxiety, health-related quality of life, and exercise capacity. Ideally, the outcome of breathlessness for intervention studies should be a comprehensive assessment that includes not only breathlessness 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 some types of intervention and by incomplete reporting in some studies. Furthermore, many of the studies had some concerns of risk of bias. In particular, nonpharmacological studies often cannot be double-blind, while pharmacological studies more often used a blinded design.

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. Studies often did not report the specific reasons for dropouts. Since most studies were very short-term, we could not determine whether patients would use or participate in these interventions for a longer period.

Our review focused on patients with advanced cancer, and findings from the broader literature on breathlessness in 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, who often have different patterns of breathlessness and multiple coexisting symptoms and treatments. A broad literature base exists on the potential harms and societal burden of medications such as opioids and anxiolytics, but specific harms may differ in patients with advanced cancer due to differences in vulnerability. 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 chronic obstructive pulmonary disease coexisting with cancer, 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 percent lung cancer patients. For some interventions, the available evidence focused on certain types of breathlessness (e.g.,



exertional breathlessness for opioids) and may not apply to episodic or chronic breathlessness 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 breathlessness issues. Some interventions (e.g., bilevel ventilation, 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 unable to report, such as those 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 breathlessness 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 breathlessness in advanced cancer outside of patients with specific indications.

Future studies should more clearly define breathlessness and the targeted breathlessness type and endpoints beyond visual analog scales. Studies generally only included patients who were cognitively intact and able to self-report. Since breathlessness can be distressing to patients who cannot self-report and their caregivers, given the importance of caregiver distress about symptoms at the end of life and breathlessness in the intensive care unit, studies including caregiver observational outcomes for patients unable to report are also needed. Our meta-analyses have the limitation of combining different types of breathlessness and populations and variations in interventions, and more focus on specific issues such as acute, chronic and exertional breathlessness, inpatient vs outpatient settings, different types and formulation of opioids, and prognosis would be useful in future studies. Including more details on population and treatment characteristics, such as prognosis, comorbid COPD, and other treatments already tried or currently being used would also be helpful for comparing and combining studies. Including a more comprehensive patient and caregiver perspective through subjective and qualitative assessment and patient- and caregiver-centered outcomes such as breathlessness goals, desired function and caregiving needs is also needed. 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. The differential costs of these interventions, and best practices for implementation, such as careful monitoring if opioids are used or how to improve access for nonpharmacologic options that require specialized training or particular clinicians, should be addressed. These patients have many other symptoms, needs and concerns, and studies should address breathlessness in this context.

Given that opioids are sometimes clinically necessary for comfort, especially when severe and 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 nonpharmacological interventions are effective for improving breathlessness in patients with advanced cancer, including fans, bilevel ventilation, acupressure/reflexology, and multicomponent interventions (behavioral/psychoeducational combined with activity/rehabilitation and integrative medicine), although some of these interventions can cause harm. Opioids and anxiolytics were not effective in improving breathlessness in patients with advanced cancer within the limits of the identified studies.



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# Abbreviations

6MWT = 6-minute walk test

Activity/Rehab = Activity/rehabilitation intervention

AHRQ = Agency for Healthcare Research and Quality

Behavioral/Psych = Behavioral and psychoeducational intervention

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

Multimodal interventions = Nonpharmacological and pharmacological interventions combined

Multicomponent = Multiple nonpharmacologic approaches

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 Analog Scale



# Appendix A. Methods

## Details of Study Selection

### Search Strategy

We searched the following databases for primary studies: PubMed, Embase®, CINAHL, ISI Web of Science, and the Cochrane Central Register of Controlled Trials. We developed a search strategy for PubMed, based on an analysis of the medical subject headings (MeSH) terms for all potentially relevant publications and text words of key articles identified *a priori*. We evaluated the search strategy by examining whether it retrieved a sample of key articles. We used a similar strategy in the other electronic sources. The detailed PubMed search strategy is listed below. We hand search the reference lists of relevant systematic reviews.

### PubMed Search Strategy

((((((((((("Complementary Therapies" [mh] OR meditation[tiab] OR acupressure [tiab] OR mindful\*[tiab] OR rehab\*[tiab] OR "music therapy" [tiab] OR "yoga" [tiab] OR rehabilitation[tiab] OR Acupuncture[mh] OR Acupuncture[tiab] OR reiki[mh] OR reiki [tiab])) OR ("Compressed Air" [mh] OR Fan [tiab] OR "compressed air"[tiab] OR "room air"[tiab] OR "room environment"[tiab] OR "water spray"[tiab] OR helium[mh] OR helium[tiab] OR heliox [tiab] OR "airway pressure"[tiab] OR "Oxygen Inhalation Therapy" [mh] OR oxygen [tiab] OR "respiratory therapy"[mh] OR ventilation [tiab] OR "pressure respiration" [tiab] OR " high flow" [tiab] OR "Bipap" [tiab] OR "cpap" [tiab])) OR ("Cognitive Behavioral Therapy"[mh] OR "Behavioral Therapy"[tiab] OR behavio\* [tiab] OR "management strategies"[tiab] OR nurse [tiab] OR nursing [tiab] OR multidisciplinary [tiab] OR clinic [tiab] OR psychosocial [tiab] OR psychoeducational [tiab] OR Psychotherapy [mh] OR psychotherapy [tiab] OR "biofeedback" [mh] OR biofeedback [tiab] OR "adaptation strategies" [tiab] OR "energy conservation" [tiab] OR "activity pacing" [tiab] OR "teaching coping" [tiab] OR "Relaxation Therapy"[mh] OR relaxation [tiab] OR "distraction therapy" [tiab])) OR (Exercise [mh] OR exercise [tiab] OR "Exercise Movement Techniques" [mh] OR "breathing techniques"[tiab] OR "breathing exercise" [tiab] OR "Tai Chi"[tiab] OR "Walking aids"[tiab] OR "mobility aids"[tiab] OR "Walking aid"[tiab] OR "mobility aid"[tiab] OR "wheelchair" [tiab] OR walker [tiab] OR electrical stimulation[mh] OR "electrical stimulation"[tiab] OR "physical therapy" [tiab] OR "occupational therapy" [tiab] OR vibration [mh] OR "chest wall vibration" [tiab] OR "chest-wall vibration" [tiab] OR "Respiratory training"[tiab] OR Rehabilitation [mh] OR "Pulmonary Rehabilitation"[tiab])) OR (((((((((((Adrenergic beta-Agonists [mh] OR Bronchodilator Agents [mh] OR albuterol [mh] OR arformoterol [mh] OR formoterol [mh] OR levalbuterol [mh] OR terbutaline [mh] OR atropine [mh] OR glycopyrrolate [mh] OR ipratropium [mh] OR scopolamine [mh] OR tiotropium [mh] OR theophylline [mh] OR aminophylline [mh] OR caffeine [mh] OR Antimuscarinics [tiab] OR Methylxanthines [tiab] OR Bronchodilator [tiab] OR albuterol [tiab] OR arformoterol [tiab] OR formoterol [tiab] OR levalbuterol [tiab] OR olodaterol [tiab] OR terbutaline [tiab] OR vilanterol [tiab] OR aclidinium [tiab] OR atropine [tiab] OR glycopyrrolate [tiab] OR ipratropium [tiab] OR scopolamine [tiab] OR tiotropium [tiab] OR umeclidinium [tiab] OR theophylline [tiab] OR aminophylline [tiab] OR caffeine [tiab])) OR ("Nebulizers and Vaporizers" [mh] OR "nebulized medications" [tiab] OR nebulizer [tiab] OR Inhaler [tiab] OR Inhalators [tiab] OR Nebulizers [tiab] OR "inhaled medications"



[tiab] OR “aerosolized medications” [tiab])) OR (Steroids [mh] OR Corticosteroids [tiab] OR beclomethasone [tiab] OR betamethasone [tiab] OR budesonide [tiab] OR ciclesonide [tiab] OR dexamethasone [tiab] OR flunisolide [tiab] OR fluticasone [tiab] OR hydrocortisone [tiab] OR methylprednisolone [tiab] OR mometasone [tiab] OR prednisone [tiab])) OR (Diuretics [mh] OR amiloride [mh] OR bumetanide [mh] OR ethacrynic acid [mh] OR furosemide [mh] OR hydrochlorothiazide [mh] OR spironolactone [mh] OR torsemide [mh] OR Diuretics [tiab] OR amiloride [tiab] OR bumetanide [tiab] OR ethacrynic acid [tiab] OR furosemide [tiab] OR hydrochlorothiazide [tiab] OR spironolactone [tiab] OR torsemide [tiab] OR metolazone [mh] OR triamterene [mh] OR indapamide [mh] OR metolazone [tiab] OR triamterene [tiab] OR indapamide [tiab])) OR (Lidocaine [mh] OR Lidocaine [tiab])) OR (Anti-Inflammatory Agents, Non-Steroidal [mh] OR Phenylpropionates [mh] OR Propionates [mh] OR celecoxib [mh] OR diclofenac [mh] OR etodolac [mh] OR fenoprofen [mh] OR flurbiprofen [mh] OR ibuprofen [mh] OR indomethacin [mh] OR ketoprofen [mh] OR ketorolac [mh] OR meloxicam [mh] OR nabumetone [mh] OR naproxen [mh] OR oxaprozin [mh] OR piroxicam [mh] OR sulindac [mh] OR tolmetin [mh] OR Phenylpropionates [tiab] OR Propionates [tiab] OR celecoxib [tiab] OR diclofenac [tiab] OR diflusalinal [tiab] OR etodolac [tiab] OR fenoprofen [tiab] OR flurbiprofen [tiab] OR ibuprofen [tiab] OR indomethacin [tiab] OR ketoprofen [tiab] OR ketorolac [tiab] OR meloxicam [tiab] OR nabumetone [tiab] OR naproxen [tiab] OR oxaprozin [tiab] OR piroxicam [tiab] OR salsalate [tiab] OR sulindac [tiab] OR tolmetin [tiab])) OR (Phenothiazines [mh] OR promethazine [mh] OR prochlorperazine [mh] OR chlorpromazine [mh] OR thioridazine [mh] OR Phenothiazines [tiab] OR promethazine [tiab] OR prochlorperazine [tiab] OR chlorpromazine [tiab] OR thioridazine [tiab])) OR (Antipsychotic Agents [mh] OR aripiprazole [mh] OR aripiprazole [tiab] OR asenapine [tiab] OR brexpiprazole [tiab] OR cariprazine [tiab] OR clozapine [mh] OR clozapine [tiab] OR haloperidol [mh] OR haloperidol [tiab] OR iloperidone [tiab] OR lurasidone [mh] OR lurasidone [tiab] OR olanzapine [mh] OR olanzapine [tiab] OR paliperidone [mh] OR paliperidone [tiab] OR pimavanserin [tiab] OR quetiapine [mh] OR quetiapine [tiab] OR risperidone [mh] OR risperidone [tiab] OR ziprasidone [tiab])) OR (Analgesics, Opioid [mh] OR opiate [tiab] OR opioid [tiab] OR codeine [mh] OR codeine [tiab] OR fentanyl [mh] OR fentanyl [tiab] OR hydrocodone [mh] OR hydrocodone [tiab] OR hydromorphone [mh] OR hydromorphone [tiab] OR morphine [mh] OR morphine [tiab] OR oxycodone [mh] OR oxycodone [tiab] OR tramadol [tiab] OR tapentadol [tiab] OR dihydrocodeine [tiab] OR buprenorphine [tiab] OR methadone [tiab] OR oxymorphone [tiab])) OR (Benzodiazepines [mh] OR Benzodiazepines [tiab] OR alprazolam [tiab] OR diazepam [tiab] OR lorazepam [tiab] OR midazolam [tiab] OR bupropion [mh] OR bupropion [tiab] OR Buspirone [mh] OR Buspirone [tiab] OR mirtazapine [mh] OR mirtazapine [tiab] OR citalopram [mh] OR citalopram [tiab] OR desvenlafaxine [mh] OR desvenlafaxine [tiab] OR duloxetine [mh] OR duloxetine [tiab] OR escitalopram [mh] OR escitalopram [tiab] OR fluoxetine [mh] OR fluoxetine [tiab] OR fluvoxamine [mh] OR fluvoxamine [tiab] OR levomilnacipran [mh] OR levomilnacipran [tiab] OR milnacipran [mh] OR milnacipran [tiab] OR paroxetine [mh] OR paroxetine [tiab] OR sertraline [mh] OR sertraline [tiab] OR venlafaxine [mh] OR venlafaxine [tiab])) OR (Anticonvulsants [mh] OR Pregabalin [mh] OR Pregabalin [tiab] OR gabapentin [mh] OR gabapentin [tiab])) AND ((Cancer [tiab] OR neoplasms [mh] OR Neoplasm [tiab] OR metastas\* [tiab] OR malignan\* [tiab] OR tumor [tiab] OR tumour\* [tiab] OR Carcinoma [tiab] OR oncology [tiab])) AND ((Dyspnea [mh] OR Dyspn\* [tiab] OR breathless\* [tiab] OR “shortness of breath” [tiab] OR “breathing difficulties” [tiab] OR “air hunger” [tiab] OR



“labored breathing” [tiab] OR “respiratory distress” [tiab])))) NOT (animals[mh] NOT Humans[mh])

## **Inclusion and Exclusion Criteria**

The eligible studies had to meet all of the following criteria: (1) adult 18 years and older with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and breathlessness; (2) received pharmacologic intervention or nonpharmacologic interventions; (3) reported outcomes of interest; (4) for effectiveness KQs (1-3) RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group and (5) published in English.

A brief overview of the PICOTS inclusion criteria is provided here.

### **Population(s):**

Patients (age  $\geq$  18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and breathlessness.

### **Interventions:**

**Non-pharmacological interventions** (KQ 1, 3, and 4)

#### **Respiratory interventions:**

- a. Airflow/ cooling: fan therapy, water spray, changing the room environment (cooling the room/opening a window)
- b. Compressed air
- c. Standard supplemental oxygen therapy (for hypoxemic and non-hypoxemic patients)
- d. Breathing gas: heliox
- e. Bilevel ventilation [Noninvasive Positive-Pressure Ventilation (Bilevel positive airway pressure (BiPAP)/ Continuous positive airway pressure (CPAP))]

#### **Behavioral and psychoeducational interventions:**

- a. Cognitive-behavioral therapy (CBT)
- b. Other behavioral interventions (may include components such as other psychosocial interventions, teaching problem-solving or coping and adaptation strategies, relaxation/distraction techniques, biofeedback, energy conservation)

#### **Activity and rehabilitation interventions:**

- a. Walking aids/mobility aids
- b. Exercise (healthcare professional-guided exercise, physical therapy, occupational therapy, aerobic exercise, non-aerobic exercise, isometric exercise, tai chi, qigong)
- c. Respiratory training
- d. Pulmonary rehabilitation
- e. Chest wall vibration
- f. Neuromuscular electrical stimulation (NMES)

#### **Integrative medicine interventions:**

- a. Acupuncture
- b. Acupressure



- c. Reiki
- d. Mindfulness
- e. Yoga
- f. Meditation
- g. Music therapy

**Combination of any of the above**

**Pharmacological interventions** (drugs approved by the Food and Drug Administration (FDA) for any indication) (KQ 2, 3, and 4).

**Any routes of administration for all drug classes are included.**

- **Bronchodilators**
  - a. Beta-adrenergic receptor agonists: albuterol, arformoterol, formoterol, indacaterol, levalbuterol, olodaterol, terbutaline, vilanterol
  - b. Antimuscarinics: acclidinium, atropine, glycopyrrolate, ipratropium, scopolamine, tiotropium, umeclidinium
  - c. Methylxanthines: theophylline, aminophylline, caffeine
- **Nebulized saline**
- **Corticosteroids:** beclomethasone, betamethasone, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone, hydrocortisone, methylprednisolone, mometasone, prednisone
- **Diuretics:** amiloride, bumetanide, ethacrynic acid, furosemide, hydrochlorothiazide, indapinide, metolazone, spironolactone, torsemide, triamterine
- **Lidocaine**
- **Non-steroidal anti-inflammatory agents:** celecoxib, diclofenac, diflusal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin
- **Phenothiazines:** promethazine, prochlorperazine, chlorpromazine, thioridazine
- **Atypical antipsychotics:** aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, ziprasidone
- **Gamma-Aminobutyric acid (GABA) analog anticonvulsants:** gabapentin, pregabalin
- **Opioids:** buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol
- **Anxiolytics**
  - a. Benzodiazepines: alprazolam, clonazepam, diazepam, lorazepam, midazolam, oxazepam, temazepam
  - b. Serotonin-norepinephrine reuptake inhibitors (SNRIs)/ Selective serotonin reuptake inhibitors (SSRIs): citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, paroxetine, sertraline, venlafaxine



c. Other: bupropion, buspirone, mirtazapine

- **Combinations of any of the above**

### **Combinations of nonpharmacologic and pharmacologic or multimodal interventions**

#### **Comparators:**

- KQ 1: Placebo, usual care, other non-pharmacological intervention or a combination of non-pharmacological interventions
- KQ 2: Placebo, usual care, other pharmacological intervention or dose or route, or a combination of pharmacological interventions
- KQ 3: Placebo, usual care, non-pharmacological interventions, pharmacologic interventions, or multimodal interventions (e.g., opioids versus respiratory training, or acupuncture versus morphine versus combination acupuncture and morphine)
- KQ 4: Any of the comparators for KQ 1, KQ 2, or KQ 3

#### **Outcomes:**

##### **Patient- or caregiver-reported, or observational symptom-related outcomes (KQ1-3)**

Caregiver-reported or observational symptom-related only if patients are unable to self-report

- Breathlessness as measured by a validated tool, which must include patient- or caregiver-reported or observational symptom-related measures of breathing difficulty or discomfort.
- Anxiety as measured by a validated tool. This tool must include patient-or caregiver-reported measures of anxiety.
- Functional status (measured by validated patient- or caregiver-reported tool)
- Health-related quality of life (general or disease-specific, measured by a validated patient- or caregiver-reported tool)

##### **Clinical or utilization health outcomes (KQ1-4)**

- Respiratory rate
- Oxygen or carbon dioxide/ bicarbonate levels
- Heart rate
- Blood pressure
- Objective measure of exercise capacity, e.g., 6-minute walk test
- Level of sedation
- Utilization outcomes linked to breathlessness: hospitalizations, intensive care unit stays, emergency room visits

##### **Patient-centered adverse effects of breathlessness treatments (KQ4)**

- 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, e.g., oxygen or masks
- Death
- Dropouts

**Timing:** Any duration of follow-up

**Setting:** Any setting

**Study design: RCTs for all KQ**

- For KQ1-3: RCTs, nonrandomized controlled trials, and observational studies with a concurrent comparison group, with at least 10 patients in each group
- For KQ 4: RCTs, nonrandomized controlled trials, observational studies with a concurrent comparison group, and prospective or retrospective cohort studies where the primary objective of the study is to evaluate harms from breathlessness treatments

## Study Selection

We used DistillerSR (Evidence Partners, 2010) to manage the screening process. DistillerSR is a web-based database management program that manages all levels of the review process. All applicable citations identified by the search strategies were uploaded to the system and reviewed in the following manner:

- i. **Abstract screening:** Two reviewers independently reviewed abstracts, which were excluded if both reviewers agreed that the article met one or more of the exclusion criteria (Table A-1). The articles did not exclude based on the study design at this level. Differences between reviewers regarding abstract eligibility were tracked and resolved through consensus adjudication. Relevant reviews, including systematic reviews and meta-analyses, were tagged for a references list search.
- ii. **Full-text screening:** Citations promoted based on abstract review underwent another independent parallel review using full-text of the articles. The differences regarding article inclusion were tracked and resolved through consensus adjudication.



**Table A-1. Study inclusion and exclusion criteria**

	<b>Inclusion</b>	<b>Exclusion</b>
<b>Population</b>	Patients (age ≥ 18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and breathlessness.	<ul style="list-style-type: none"> <li>• Animal studies</li> <li>• Studies with patients under 18 years of age</li> <li>• Mixed population - Less than 50% of the population consists of cancer patients OR study does not report stratified data</li> </ul>
<b>Interventions</b>	All studies must evaluate an intervention of interest as defined by KQ1-4*	<ul style="list-style-type: none"> <li>• No intervention of interest</li> <li>• Endoscopic or surgical interventions (stent, laser, argon-beamer)</li> </ul>
<b>Comparisons</b>	For KQ 1-3, the comparison could be no intervention or one or more of the interventions of interest*	<ul style="list-style-type: none"> <li>• For KQ 1-3, exclude studies that do not report a comparison group.</li> </ul>
<b>Outcomes</b>	All studies must evaluate patient- or caregiver-reported breathlessness (KQ1-3) or an included harm (KQ4)*	<ul style="list-style-type: none"> <li>• Exclude studies that do not report any outcomes of interest.</li> <li>• Reporting only clinical and utilization outcomes</li> <li>• Reporting only selected harms of interest unless primary objective of the study was to assess harms</li> </ul>
<b>Type of Study</b>	<p>For KQ1-3: RCTs and nonrandomized controlled trials and observational trials with a concurrent comparison group, with at least 10 patients in each arm</p> <p>For KQ 4: RCTs, nonrandomized controlled trials, observational studies with a concurrent comparison group with at least 10 patients in each arm, and prospective or retrospective cohort studies where the primary objective of the study is to evaluate harms from breathlessness treatments.</p>	<ul style="list-style-type: none"> <li>• KQ 1 – KQ 3: <ul style="list-style-type: none"> <li>◦ Exclude trials that are not controlled</li> <li>◦ Single arm studies [pre-post]</li> </ul> </li> <li>• KQ 4: Exclude case control studies, case reports, and case series</li> <li>• Publications with no original data (e.g., editorials, letters, comments, reviews)</li> <li>• Non-English publications</li> <li>• Full text not presented or unavailable, abstracts only</li> </ul>

KQ =key question, RCT =randomized controlled trial

\* Please see PICOTS inclusion criteria

## Data Extraction

We used a systematic approach to extract all data to minimize the risk of bias in this process. We created and pilot tested standardized forms for data extraction. Each article underwent double review by the study investigators for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. A third reviewer audited a random sample of articles by the first two reviewers to ensure consistency in the data abstraction of the articles.

For all articles, reviewers extracted information on general study characteristics (e.g., study design, study period, and follow-up), study participant characteristics, eligibility criteria, interventions, outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability. We completed the data abstraction process using



forms created in Excel (Microsoft, Redmond, WA). The Excel files were used to maintain the data and to create detailed evidence tables and summary tables .

## Clinically Important Difference

Although a minimally clinically important difference (MCID) in breathlessness intensity has not been formally established, there are data available to help guide this determination. In heart failure, studies have identified a difference on the VAS between 10 and 21.1 mm as clinically significant.<sup>1-3</sup> Similarly, data for chronic refractory breathlessness and COPD suggest a difference of 10mm on the VAS or 0.8 on the Borg scale as clinically.<sup>4, 5</sup> In a cancer population, data from a study of breathlessness from malignant pleural effusion suggest a difference on the VAS of 19 mm is clinically significant and a population of advanced cancer patients admitted to a palliative care unit considered a difference on the NRS of 2.1 to be clinically important.<sup>6, 7</sup> Given the available data, we considered a difference on the VAS of 10 mm or greater as clinically meaningful, which is equivalent to a standardized mean difference of 0.35. This is applicable for data on breathlessness outcomes.

## Risk of Bias Assessment of Individual Studies

Two reviewers independently assessed risk of bias for each study. For RCTs, we used the Cochrane Risk of Bias Tool, Version 2.<sup>8</sup> For non-randomized studies, we used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I tool).<sup>9</sup> Differences between reviewers were resolved through consensus adjudication.

## Grading the Strength of the Body of Evidence

At the completion of our review, we graded the strength of evidence on *key outcomes*, including breathlessness, anxiety, health-related quality of life, and exercise capacity by using the grading scheme recommended by the Agency for Healthcare Research and Quality Methods Guide for Conducting Comparative Effectiveness Reviews.<sup>10</sup>

Following this standard approach, for each key outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings/results across studies.

The overall strength of evidence for each key outcome was determined based on assessment of five domains:

1. Study limitations (assessment of risk of bias and overall methodological quality of study design and conduct -graded low, moderate, high);
2. Consistency of results across studies (the degree to which included studies find the same direction or similar magnitude of effect, -graded consistent, inconsistent, or for single studies, unknown);
3. Directness of the evidence linking the interventions with outcomes;
4. Effect estimate precision (based on the size of the body of evidence, number of events, and confidence intervals -graded precise or imprecise); and
5. Reporting bias (the likelihood that some findings were selectively published -graded suspected or undetected).

We assessed the aggregate risk of bias of studies and integrated these assessments into a qualitative assessment of the summary risk of bias score. In evaluating consistency, we



qualitatively considered giving greater weight to those with large sample sizes if they were accompanied by one to two other conflicting studies. If all the studies in an evidence base showed a similar direction of effect, we rated the evidence base as consistent. We rated single studies as consistency unknown. We considered all key outcomes direct (intervention was directly linked to the outcomes). We graded evidence as being precise when results had low degree of uncertainty.

We assigned the final strength of evidence grade by evaluating and qualitatively considering the assessments of the above domains, including the effect size in terms of the MCID, and the global assessment of the results across studies. We assigned a strength of evidence rating of high, moderate, low, or insufficient for each key outcome after discussion by two reviewers and by consensus with other team members as needed [Table A-2]. Each strength of evidence domain was considered qualitatively across a continuum, even though the individual domains were reported categorically. Hence, the final strength of evidence for two outcomes could be different despite them having similar categorization of the individual domains.

**Table A-2. Definitions of the grades of overall strength of evidence**

<b>Grade</b>	<b>Definition</b>
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

## Peer Review and Public Commentary

Experts in oncology, palliative care and individuals representing stakeholder and user communities were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided their comments. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We addressed all reviewer comments, revised the text as appropriate. A disposition of comments table of peer and public comments will be posted on the EHC website 3 months after the Agency posts the final systematic review.

## Definitions

Definitions of common terms used in the report.



**Table A-3. Definition of terms**

<b>Term</b>	<b>Definition</b>
Acute breathlessness	New and sudden (short-term, onset and duration over minutes to hours to days) development of breathlessness in the absence of exertion, or new and sudden worsening of existing breathlessness.
Advanced cancer	The American Cancer Society defines advanced cancer as "cancers that cannot be cured", and metastatic cancer as tumors that "have usually spread from where they started to other parts of the body". <sup>11</sup> However, not all advanced cancers are metastatic. For example, brain tumors may be considered advanced because they are not curable, and life-threatening, even in the absence of metastasis. For the purposes of our study, we included studies that includes patients with advanced cancer defined variably as stage 3 or 4 cancer, locally advanced, recurrent or metastatic cancer, refractory or metastatic cancer, end-stage cancer, cancer patients receiving hospice care, or terminal cancer.
Breathlessness	A subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. <sup>12</sup>
Chronic breathlessness	Presence of breathlessness over a longer term (over weeks to months) in the absence of exertion.
Exertional breathlessness	Shortness of breath is present with exercise and improves with rest. Exercise is defined here as any physical exertion, which increases metabolic oxygen demand above the body's ability to compensate. <sup>13</sup>
High Flow Nasal Cannula (HFNC)	Delivers a humidified, heated, air oxygen blend (allowing from 21% to 100% fraction of inspired oxygen) generating up to 60 Liters/minute flow rates through a large diameter nasal cannula.
Hypoxemia	Oxygen saturation (SpO <sub>2</sub> ) <90% while breathing room air at rest. <sup>14-16</sup>
Long-term followup	Followup of weeks to months.
Low-dose opioids	As defined by the studies that used this terminology: 25 percent of the current four-hour total of opioid (low dose) compared with 50 percent (high dose). <sup>17</sup> 15 to 25 percent of the total opioid dose (low dose) as compared to 35 to 45 percent of the total opioid dose (high dose). <sup>18</sup>
Multi-component intervention	Intervention that can include a range of components combining more than one type 'intervention subgroups of the PICOTS framework.
Short term followup	Followup of minutes to a few weeks.
Standard supplemental oxygen	Conventional oxygen therapy delivered via nasal cannula or face masks.
Usual care	Several non-pharmacologic studies were unblinded and patients in the non-intervention (control) arm received routine medical care as per usual standard of care. In these studies where no placebo or sham intervention was performed in the control group, we described their care as "usual care".



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7. Mercadante S, Adile C, Aielli F, et al. Personalized Goal for Dyspnea and Clinical Response in Advanced Cancer Patients. *J Pain Symptom Manage*. 2019 Jan;57(1):79-85. doi: 10.1016/j.jpainsymman.2018.10.492. PMID: 30336213.
8. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:14898.
9. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.
10. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF Agency for Healthcare Research and Quality. Rockville, MD: 2014. [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)
11. Haun MW, Estel S, Rücker G, et al. Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev*. 2017 Jun 12;6(6):Cd011129. doi: 10.1002/14651858.CD011129.pub2. PMID: 28603881.
12. Walling AM, Weeks JC, Kahn KL, et al. Symptom prevalence in lung and colorectal cancer patients. *J Pain Symptom Manage*. 2015 Feb;49(2):192-202. doi: 10.1016/j.jpainsymman.2014.06.003. PMID: 24973624.
13. Sharma S, Hashmi MF, M. B. Dyspnea on Exertion (DOE). *StatPearls*. Vol. Treasure Island, FL. StatPearls Publishing; 2020.
14. Booth S, Kelly MJ, Cox NP, et al. Does oxygen help dyspnea in patients with cancer? *Am J Respir Crit Care Med*. 1996 May;153(5):1515-8. doi: 10.1164/ajrccm.153.5.8630595. PMID: 8630595.
15. Philip J, Gold M, Milner A, et al. A randomized, double-blind, crossover trial of the effect of oxygen on dyspnea in patients with advanced cancer. *J Pain Symptom Manage*. 2006 Dec;32(6):541-50. doi: 10.1016/j.jpainsymman.2006.06.009. PMID: 17157756.
16. Bruera E, de Stoutz N, Velasco-Leiva A, et al. Effects of oxygen on dyspnoea in hypoxaemic terminal-cancer patients. *Lancet*. 1993 Jul 3;342(8862):13-4. doi: 10.1016/0140-6736(93)91880-u. PMID: 8100289.



17. Allard P, Lamontagne C, Bernard P, et al. How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial. *J Pain Symptom Manage*. 1999 Apr;17(4):256-65. PMID: 10203878.
18. Hui D, Hernandez F, Larsson L, et al. Prophylactic Fentanyl Sublingual Spray for Episodic Exertional Dyspnea in Cancer Patients: A Pilot Double-Blind Randomized Controlled Trial. *J Pain Symptom Manage*. 2019 Jul 2doi: 10.1016/j.jpainsymman.2019.06.024. PMID: 31276809.



## Appendix B. Excluded Studies

1. Comparison of the quality of life of cancer patients with pain treated with oral controlled-release morphine and oxycodone and transdermal buprenorphine and fentanyl. Current pharmaceutical design. 2019doi: 10.2174/1381612825666190717091230. PMID: CN-02003074. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
2. Abernethy AP, McDonald CF, Frith PA, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet*. 2010 Sep 4;376(9743):784-93. doi: 10.1016/s0140-6736(10)61115-4. PMID: 20816546. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
3. Abernethy AP, Wheeler JL, Currow DC. Palliative Care and Dyspnea Management in Patients with Hematological Malignancies and Acute Respiratory Failure; 2011. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
4. Ahmedzai SH, Laude E, Robertson A, et al. A double-blind, randomised, controlled Phase II trial of Heliox28 gas mixture in lung cancer patients with dyspnoea on exertion. *Br J Cancer*. 2004 Jan 26;90(2):366-71. doi: 10.1038/sj.bjc.6601527. PMID: 14735178. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
5. Akashi M. Management of dyspnea with central airway obstruction in palliative cancer patients: Symptomatic therapy with combined doses of opioids and glucocorticoids. *Teikyo Medical Journal*. 2012;35(6):301-14. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
6. Alonso-Babarro A, Varela-Cerdeira M, Torres-Vigil I, et al. At-home palliative sedation for end-of-life cancer patients. *Palliat Med*. 2010 Jul;24(5):486-92. doi: 10.1177/0269216309359996. PMID: 20133320. **-Intent of the intervention is NOT to alleviate dyspnea**
7. Arving C, Sjoden PO, Bergh J, et al. Individual psychosocial support for breast cancer patients: a randomized study of nurse versus psychologist interventions and standard care. *Cancer Nurs*. 2007 May-Jun;30(3):E10-9. doi: 10.1097/01.ncc.0000270709.64790.05. PMID: 17510577. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
8. Azoulay E, Canet E, Raffoux E, et al. Dexamethasone in patients with acute lung injury from acute monocytic leukaemia. *Eur Respir J*. 2012 Mar;39(3):648-53. doi: 10.1183/09031936.00057711. PMID: 21828031. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
9. Bade BC, Brooks MC, Nietert SB, et al. Assessing the Correlation Between Physical Activity and Quality of Life in Advanced Lung Cancer. *Integr Cancer Ther*. 2018 Mar;17(1):73-9. doi: 10.1177/1534735416684016. PMID: 28024420. **-Intent of the intervention is NOT to alleviate dyspnea**
10. Barinow-Wojewódzki A, Laurentowska M, Domaszewska K, et al. Effects of rehabilitation on physical efficiency in patients with lung cancer evaluated by means of the 6-minute walking test. *Fizjoterapia*. 2008;16(3):36-47. doi: 10.2478/v10109-009-0027-6. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**



11. Bausewein C, Booth S, Gysels M, et al. Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. *BMC Palliat Care*. 2010 Oct 19;9:22. doi: 10.1186/1472-684x-9-22. PMID: 20958972. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
12. Bayati M, Molavynejad S, Taheri N, et al. Investigating the effect of Integrated Educational Program on the Quality of Life among Cancer Patients: A Clinical Trial Study. *Asian Pac J Cancer Prev*. 2019 Nov 1;20(11):3457-63. doi: 10.31557/apjcp.2019.20.11.3457. PMID: 31759372. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
13. Baydur A. Nebulized morphine - A convenient and safe alternative to dyspnea relief? *Chest*. 2004 Feb;125(2):363-5. PMID: 14769709. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
14. Benitez-Rosario MA, Martin AS, Feria M. Oral transmucosal fentanyl citrate in the management of dyspnea crises in cancer patients. *J Pain Symptom Manage*. 2005 Nov;30(5):395-7. doi: 10.1016/j.jpainsymman.2005.10.002. PMID: 16310612. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
15. Benitez-Rosario MA, Martin AS, Feria M. Oral transmucosal fentanyl citrate in the management of dyspnea crisis in cancer patients. *Journal of Pain and Symptom Management*. 2005 Nov;30(5):395-7. doi: 10.1016/j.jpainsymman.2005.10.002. PMID: 16310612. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
16. Bilgic S, Acaroglu R. Effects of Listening to Music on the Comfort of Chemotherapy Patients. *West J Nurs Res*. 2017 Jun;39(6):745-62. doi: 10.1177/0193945916660527. PMID: 27515501. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
17. Booth S, Galbraith S, Ryan R, et al. The importance of the feasibility study: Lessons from a study of the hand-held fan used to relieve dyspnea in people who are breathless at rest. *Palliative Medicine*. 2016 May;30(5):504-9. PMID: WOS:000374680000010. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
18. Booth S, Moffat C, Farquhar M, et al. Developing a Breathlessness Intervention Service for Patients with Palliative and Supportive Care Needs, Irrespective of Diagnosis. *J Palliat Care*. 2011 Spr;27(1):28-36. PMID: WOS:000293483700006. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
19. Booth S, Wade R. Oxygen or air for palliation of breathlessness in advanced cancer. *J R Soc Med*. 2003 May;96(5):215-8. doi: 10.1258/jrsm.96.5.215. PMID: 12724429. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
20. Bredin M, Corner J, Krishnasamy M, et al. Multicentre randomised controlled trial of nursing intervention for breathlessness in patients with lung cancer. *BMJ*. 1999 Apr 3;318(7188):901-4. doi: 10.1136/bmj.318.7188.901. PMID: 10102851. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
21. Bulbul Y, Ozlu T, Arinc S, et al. Assessment of palliative care in lung cancer in Turkey (ASPECT study). *European Respiratory Journal*. 2015 Sep 1;46 PMID: WOS:000451979407036. **-No full report (e.g. conference or meeting abstract)**
22. Bushunow PW, Roscoe JA, Dudgeon DJ, et al. Buspirone treatment of dyspnea in outpatients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program (URCC CCOP) study. *Journal of clinical oncology*. 2011;29(15 SUPPL. 1) PMID: CN-01034146. **-No full report (e.g. conference or meeting abstract)**



23. Cabezon-Gutierrez L, Delgado-Mingorance I, Nabal-Vicuna M, et al. Observational study to analyze patterns of treatment of breakthrough dyspnea in cancer patients in clinical practice. *Medwave*. 2018 Jun 12;18(3):e7211. doi: 10.5867/medwave.2018.03.7211. PMID: 29920510. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
24. Cerchietti LC, Navigante AH, Castro MA. Oral morphine versus oral midazolam as upfront therapy to relief dyspnea in ambulatory cancer patients while its underlying cause is sought or treated. *Journal of Clinical Oncology*. 2008 May;26(15)doi: 10.1200/jco.2008.26.15\_suppl.9585. PMID: WOS:000208457403553. **-No full report (e.g. conference or meeting abstract)**
25. Chai CS, Liam CK, Pang YK, et al. Dyspnea improvement in patients with lung diseases in a single session of mindful breathing: a randomized controlled study. *Respirology (Carlton, Vic.)*. 2018;23:197-8. doi: 10.1111/resp.13420. PMID: CN-01763570. **-No full report (e.g. conference or meeting abstract)**
26. Chai CS, Tan SB, Ng DLC, et al. A randomized controlled trial of mindfulness breathing exercise in patients with advanced lung cancer. *Annals of oncology*. 2018;29doi: 10.1093/annonc/mdy440.005. PMID: CN-01934510. **-No full report (e.g. conference or meeting abstract)**
27. Charalambous A, Molassiotis A, Summers Y, et al. Use of inspiratory muscle training in managing dyspnoea in lung cancer patients. *Journal of thoracic oncology*. 2017;12(1):S206-S8. PMID: CN-01733901. **-No full report (e.g. conference or meeting abstract)**
28. Clemens KE, Klaschik E. Dyspnoea associated with anxiety-symptomatic therapy with opioids in combination with lorazepam and its effect on ventilation in palliative care patients. *Supportive Care in Cancer*. 2011 Dec;19(12):2027-33. PMID: 21153667. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
29. Clemens KE, Klaschik E. Treatment of dyspnoea in patients receiving palliative care: Nasal delivery of oxygen compared with opioid administration. *Deutsche Medizinische Wochenschrift*. 2007;132(38):1939-43. doi: 10.1055/s-2007-985621. **-Not in English**
30. Clemens KE, Quednau I, Klaschik E. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. *Support Care Cancer*. 2009 Apr;17(4):367-77. doi: 10.1007/s00520-008-0479-0. PMID: 18719948. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
31. Coffin JR, Kerigan A, Russell SA, et al. Assessment of a dyspnea clinic for patients with thoracic malignancies. *Journal of Clinical Oncology*. 2014 May;32(15) PMID: WOS:000358613201638. **-No full report (e.g. conference or meeting abstract)**
32. Cole C, Peppone LJ, Kleckner I, et al. Effects of exercise on dyspnea and cancer-related fatigue in patients with prostate cancer. *Journal of clinical oncology*. 2017;35(15) PMID: CN-01398345. **-No full report (e.g. conference or meeting abstract)**
33. Congleton J, Muers MF. The incidence of airflow obstruction in bronchial carcinoma, its relation to breathlessness, and response to bronchodilator therapy. *Respir Med*. 1995 Apr;89(4):291-6. PMID: 7597269. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**



34. Connors S, Graham S, Peel T. An evaluation of a physiotherapy led non-pharmacological breathlessness programme for patients with intrathoracic malignancy. *Palliat Med.* 2007 Jun;21(4):285-7. doi: 10.1177/0269216307079172. PMID: 17656404. - **Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
35. Cuervo Pinna MA. A randomized crossover clinical trial to evaluate the efficacy of oral transmucosal fentanyl citrate in the treatment of dyspnea on exertion in patients with advanced cancer. *J Pain Symptom Manage.* 2014 Jun;47(6):e4-5. doi: 10.1016/j.jpainsymman.2013.12.235. PMID: 24685724. -**No full report (e.g. conference or meeting abstract)**
36. Currow DC, Agar M, Smith J, et al. Does palliative home oxygen improve dyspnoea? A consecutive cohort study. *Palliat Med.* 2009 Jun;23(4):309-16. doi: 10.1177/0269216309104058. PMID: 19304806. -**No patient reported outcomes and does not apply to harms KQ4**
37. Currow DC, Plummer J, Frith P, et al. Can we predict which patients with refractory Dyspnea will respond to opioids? *Journal of Palliative Medicine.* 2007 Oct;10(5):1031-6. PMID: 17985956. -**Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
38. Dai J, Liao N, Shi J, et al. Study of prevalence and influencing factors of depression in tumor patients and the therapeutic effects of fluoxetine. *Eur Rev Med Pharmacol Sci.* 2017 Nov;21(21):4966-74. PMID: 29164561. -**Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
39. Davis C, Penn K, A'Hern R, et al. Single dose randomised controlled trial of nebulised morphine in patients with cancer related breathlessness. *Pall med.* 1996;10:64-5. PMID: CN-01155381. -**No full report (e.g. conference or meeting abstract)**
40. Dhillon H, Bell M, Van Der Ploeg H, et al. The impact of physical activity on fatigue and quality of life in lung cancer patients: a randomised controlled trial. *Asia-pacific journal of clinical oncology.* 2015;11:70-. doi: 10.1111/ajco.12432. PMID: CN-01106570. -**No full report (e.g. conference or meeting abstract)**
41. Do J, Cho Y, Jeon J. Effects of a 4-week multimodal rehabilitation program on quality of life, cardiopulmonary function, and fatigue in breast cancer patients. *J Breast Cancer.* 2015 Mar;18(1):87-96. doi: 10.4048/jbc.2015.18.1.87. PMID: 25834616. -**Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
42. Doorley J, Hobbs M, Delaney E, et al. The role of nebulized opioids in managing terminal dyspnea: implications for the clinical nurse specialist. *Clinical nurse specialist CNS.* 2003 2003-Jan;17(1):19-21. PMID: 12544116. -**No original data (systematic reviews, meta-analysis, editorial, commentary)**
43. Edbrooke L, Denehy L, Granger CL, et al. Home-based rehabilitation in inoperable non-small cell lung cancer—the patient experience. *Supportive Care in Cancer.* 2020;28(1):99-112. doi: 10.1007/s00520-019-04783-4. -**Intent of the intervention is NOT to alleviate dyspnea**
44. Elsayem A, Bruera E. High-dose corticosteroids for the management of dyspnea in patients with tumor obstruction of the upper airway. *Support Care Cancer.* 2007 Dec;15(12):1437-9. doi: 10.1007/s00520-007-0305-0. PMID: 17636344. -**Case series or case reports**
45. Elsayem A, Curry Iii E, Boohene J, et al. Use of palliative sedation for intractable symptoms in the palliative care unit of a comprehensive cancer center. *Support Care Cancer.* 2009 Jan;17(1):53-9. doi: 10.1007/s00520-008-0459-4. PMID: 18461370. -**Intent of the intervention is NOT to alleviate dyspnea**



46. Eucetr GB. Prospective randomised controlled trial to investigate the effectiveness of inhalers for the relief of breathlessness in patients with lung cancer and COPD - Airway disease optimisation of pharmaco-therapy in lung cancer. <http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2010-021412-42-GB>. 2010 PMID: CN-01830072. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
47. Feinstein M. Acupuncture for Shortness of Breath in Cancer Patients. Pdq, 1 r21 at01029-01, nct00067691. 2004 PMID: CN-00462671. **- Other: No intervention**
48. Ferreira DH, Silva JP, Quinn S, et al. Blinded Patient Preference for Morphine Compared to Placebo in the Setting of Chronic Refractory Breathlessness--An Exploratory Study. J Pain Symptom Manage. 2016 Feb;51(2):247-54. doi: 10.1016/j.jpainsymman.2015.10.005. PMID: 26598037. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
49. Follwell M, Burman D, Le LW, et al. Phase II study of an outpatient palliative care intervention in patients with metastatic cancer. J Clin Oncol. 2009 Jan 10;27(2):206-13. doi: 10.1200/jco.2008.17.7568. PMID: 19064979. **-Intent of the intervention is NOT to alleviate dyspnea**
50. Foote M, Sexton DL, Pawlik L. Dyspnea: a distressing sensation in lung cancer. Oncol Nurs Forum. 1986 Sep-Oct;13(5):25-31. PMID: 3638716. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
51. Galbraith S, Fagan P, Perkins P, et al. Does the Use of a Handheld Fan Improve Chronic Dyspnea? A Randomized, Controlled, Crossover Trial. Journal of Pain and Symptom Management. 2010;39(5):831-8. doi: 10.1016/j.jpainsymman.2009.09.024. **- Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
52. Giasson M, Bouchard L. Effect of therapeutic touch on the well-being of persons with terminal cancer. J Holist Nurs. 1998 Sep;16(3):383-98. doi: 10.1177/089801019801600307. PMID: 9849260. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
53. Gomutbutra P, O'Riordan DL, Pantilat SZ. Management of moderate-to-severe dyspnea in hospitalized patients receiving palliative care. J Pain Symptom Manage. 2013 May;45(5):885-91. doi: 10.1016/j.jpainsymman.2012.05.004. PMID: 22940561. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
54. Greer JA, MacDonald JJ, Vaughn J, et al. Pilot Study of a Brief Behavioral Intervention for Dyspnea in Patients With Advanced Lung Cancer. J Pain Symptom Manage. 2015 Dec;50(6):854-60. doi: 10.1016/j.jpainsymman.2015.06.010. PMID: 26166181. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
55. Grimberty D, Lubin O, de Monte M, et al. [Dyspnea and morphine aerosols in the palliative care of lung cancer]. Rev Mal Respir. 2004 Dec;21(6 Pt 1):1091-7. PMID: 15767953. **-Not in English**
56. Grimberty D, Lubin O, De Monte M, et al. Morphine aerosols in the palliative care of lung cancer. Revue des Maladies Respiratoires. 2004;21(6 I):1091-7. PMID: 15767953. **-Not in English**
57. Harrison TJR. A comparison of the effectiveness of oral lorazepam and placebo in relieving breathlessness associated with advanced cancer. (MSC thesis, bristol university, 2004). 2004 PMID: CN-01573968. **-Other: Protocol**



58. Higginson IJ, Bausewein C, Reilly CC, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med*. 2014 Dec;2(12):979-87. doi: 10.1016/s2213-2600(14)70226-7. PMID: 25465642. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
59. Higginson IJ, Wilcock A, Johnson MJ, et al. Randomised, double-blind, multicentre, mixed-methods, dose-escalation feasibility trial of mirtazapine for better treatment of severe breathlessness in advanced lung disease (BETTER-B feasibility). *Thorax*. 2020 Feb;75(2):176-9. doi: 10.1136/thoraxjnl-2019-213879. PMID: 31915308. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
60. Hoyal C, Grant J, Chamberlain F, et al. Improving the management of breathlessness using a clinical effectiveness programme. *Int J Palliat Nurs*. 2002 Feb;8(2):78-87. doi: 10.12968/ijpn.2002.8.2.10243. PMID: 11873237. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
61. Hu WY, Chiu TY, Cheng SY, et al. Morphine for dyspnea control in terminal cancer patients: is it appropriate in Taiwan? *J Pain Symptom Manage*. 2004 Oct;28(4):356-63. doi: 10.1016/j.jpainsymman.2004.01.004. PMID: 15471653. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
62. Hui D, Kilgore K, Frisbee-Hume S, et al. Dexamethasone for dyspnea in cancer patients: a double-blind, randomized controlled trial. *Supportive care in cancer*. 2016;24(1):S54-. doi: 10.1007/s00520-016-3209-z. PMID: CN-01754401. **-No full report (e.g. conference or meeting abstract)**
63. Hui D, Kilgore K, Park M, et al. Impact of prophylactic fentanyl pectin nasal spray (FPNS) on exercise-induced episodic dyspnea in cancer patients: a double-blind, randomized controlled trial. *Supportive care in cancer*. 2016;24(1):S185-S6. doi: 10.1007/s00520-016-3209-z. PMID: CN-01723274. **-No full report (e.g. conference or meeting abstract)**
64. Hui D, Larsson L, Thomas S, et al. Effect of high flow oxygen on exertional dyspnea in cancer patients: A double-blind randomized clinical trial. *Journal of Clinical Oncology*. 2019 May;37(15) PMID: WOS:000487345804268. **-No full report (e.g. conference or meeting abstract)**
65. Hui D, Morgado M, Chisholm GB, et al. High-flow oxygen (HFO) and bilevel positive airway pressure (BiPAP) for refractory dyspnea in patients with advanced cancer: a randomized controlled trial. *Journal of clinical oncology*. 2013;31(15) PMID: CN-01007451. **-No full report (e.g. conference or meeting abstract)**
66. Hui D, Xu A, Frisbee-Hume S, et al. Prophylactic subcutaneous fentanyl for exercise-induced breakthrough dyspnea: a preliminary double-blind, randomized controlled trial. *Supportive care in cancer*. 2013;21:S191-. doi: 10.1007/s00520-013-1798-3. PMID: CN-01011778. **-No full report (e.g. conference or meeting abstract)**
67. Ichikawa T, Yokoba M, Horimizu Y, et al. Respiratory muscle strength, exercise capacity, and dyspnea during pulmonary rehabilitation after lobectomy in patients with non-small cell lung cancer. *Respirology*. 2018 Nov;23:166-. PMID: WOS:000456217200434. **-No full report (e.g. conference or meeting abstract)**
68. Igarashi H, Fukushi M, Nago N. Oxygen use and survival in patients with advanced cancer and low oxygen saturation in home care: a preliminary retrospective cohort study. *BMC Palliat Care*. 2020 Jan 3;19(1):3. doi: 10.1186/s12904-019-0511-9. PMID: 31900147. **-Intent of the intervention is NOT to alleviate dyspnea**



69. Jastrzebski D, Maksymiak M, Kostorz S, et al. Pulmonary Rehabilitation in Advanced Lung Cancer Patients During Chemotherapy. *Adv Exp Med Biol*. 2015;861:57-64. doi: 10.1007/5584\_2015\_134. PMID: 26017725. **-Study with less than ten patients in the main intervention group**
70. Jastrzebski D, Rutkowska A, Rutkowski S, et al. Short-time exercise-induced rehabilitation in non-small cell lung cancer patients during in-hospital chemotherapy treatment: a randomized controlled trial. *European respiratory journal*. 2017;50doi: 10.1183/1393003.congress-2017.OA4671. PMID: CN-01794097. **-No full report (e.g. conference or meeting abstract)**
71. Ji W, Kwon H, Lee S, et al. Mobile Health Management Platform-Based Pulmonary Rehabilitation for Patients With Non-Small Cell Lung Cancer: Prospective Clinical Trial. *JMIR Mhealth Uhealth*. 2019 Jun 21;7(6):e12645. doi: 10.2196/12645. PMID: 31228180. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
72. Johnson MJ, Bland JM, Oxberry SG, et al. Opioids for chronic refractory breathlessness: patient predictors of beneficial response. *Eur Respir J*. 2013 Sep;42(3):758-66. doi: 10.1183/09031936.00139812. PMID: 23258776. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
73. Johnson MJ, Booth S, Currow DC, et al. A Mixed-Methods, Randomized, Controlled Feasibility Trial to Inform the Design of a Phase III Trial to Test the Effect of the Handheld Fan on Physical Activity and Carer Anxiety in Patients With Refractory Breathlessness. *J Pain Symptom Manage*. 2016 May;51(5):807-15. doi: 10.1016/j.jpainsymman.2015.11.026. PMID: 26880253. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
74. Johnson MJ, Kanaan M, Richardson G, et al. A randomised controlled trial of three or one breathing technique training sessions for breathlessness in people with malignant lung disease. *BMC Med*. 2015 Sep 7;13:213. doi: 10.1186/s12916-015-0453-x. PMID: 26345362. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
75. Johnson MJ, Sbizzera I, Fairhurst C, et al. No excess harms from sustained-release morphine: a randomised placebo-controlled trial in chronic breathlessness. *BMJ Support Palliat Care*. 2019 Nov 12doi: 10.1136/bmjspcare-2019-002009. PMID: 31719052. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
76. Kako J, Kajiwaru K, Noto H, et al. Response to "Prophylactic Fentanyl Sublingual Spray for Episodic Exertional Dyspnea in Cancer Patients: A Pilot Double-Blind Randomized Controlled Trial". *J Pain Symptom Manage*. 2019 Jul 26doi: 10.1016/j.jpainsymman.2019.07.020. PMID: 31356962. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
77. Kako J, Kobayashi M, Oosono Y, et al. FAN THERAPY FOR THE RELIEF OF DYSPNEA IN MALIGNANT AND NON-MALIGNANT DISEASES. *Oncology Nursing Forum*. 2019 Mar;46(2) PMID: WOS:000461140000600. **-No full report (e.g. conference or meeting abstract)**
78. Kim HS, Kim MK, Lee M, et al. Effect of Red Ginseng on Genotoxicity and Health-Related Quality of Life after Adjuvant Chemotherapy in Patients with Epithelial Ovarian Cancer: A Randomized, Double Blind, Placebo-Controlled Trial. *Nutrients*. 2017 Jul 19;9(7)doi: 10.3390/nu9070772. PMID: 28753932. **-Intent of the intervention is NOT to alleviate dyspnea**



79. Kim JW, Park EY. Self-management of oxygen and bronchodilators to relieve the dyspnoea of lung cancer with pneumoconiosis. *International Journal of Palliative Nursing*. 2020;26(4):167-74. doi: 10.12968/ijpn.2020.26.4.167. PMID: 143103289. Language: English. Entry Date: In Process. Revision Date: 20200511. Publication Type: Article. **-No patient reported outcomes and does not apply to harms KQ4**
80. Kim YH, Okuda C, Sakamori Y, et al. Continuous morphine infusion for end-stage lung cancer patients. *Oncol Lett*. 2013 Mar;5(3):972-4. doi: 10.3892/ol.2012.1101. PMID: 23426526. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
81. Kohara H, Ueoka H, Aoe K, et al. Effect of nebulized furosemide in terminally ill cancer patients with dyspnea. *J Pain Symptom Manage*. 2003 Oct;26(4):962-7. PMID: 14575057. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
82. Krajnik M, Zylicz Z. Are patients with advanced diseases capable of inhaling drugs by dry powder inhaler? Multicenter, open pilot study of patients suffering from dyspnoea at rest. *Polska Medycyna Paliatywna*. 2006;5(4):162-6. **-Not in English**
83. Lai WS, Chao CS, Yang WP, et al. Efficacy of guided imagery with theta music for advanced cancer patients with dyspnea: a pilot study. *Biol Res Nurs*. 2010 Oct;12(2):188-97. doi: 10.1177/1099800409347556. PMID: 20453018. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
84. Lemiale V, Mokart D, Mayaux J, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. *Crit Care*. 2015 Nov 2;19:380. doi: 10.1186/s13054-015-1097-0. PMID: 26521922. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
85. Leppert W, Majkowicz M. Assessment of analgesia and adverse effects of controlled release tramadol and dihydrocodeine in patients with cancer pain - Based on a modified ESAS. *Wspolczesna Onkologia*. 2008;12(5):246-54. **-Not in English**
86. Leppert W, Nosek K. Comparison of the quality of life of cancer patients with pain treated with oral controlled-release morphine and oxycodone and transdermal buprenorphine and fentanyl. *Curr Pharm Des*. 2019 Jul 16doi: 10.2174/1381612825666190717091230. PMID: 31333114. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
87. Lim Y, Lee H, Kim DH, et al. [Applying Extended Theory of Planned Behavior for Lung Cancer Patients Undergone Pulmonary Resection: Effects on Self-Efficacy for Exercise, Physical Activities, Physical Function, and Quality of Life]. *J Korean Acad Nurs*. 2020 Feb;50(1):66-80. doi: 10.4040/jkan.2020.50.1.66. PMID: 32131074. **-Not in English**
88. Liu F, Wang ML, Yuan HH, et al. Effects of morphine, methylprednisolone and aminophylline on management of dyspnea in patients with advanced cancer. *Journal of Shanghai Jiaotong University (Medical Science)*. 2013;33(6):823-6. doi: 10.3969/j.issn.1674-8115.2013.06.025. **-Not in English**



89. Lopez G, Chaoul A, Powers-James C, et al. A Pragmatic Evaluation of Symptom Distress After Group Meditation for Cancer Patients and Caregivers: A Preliminary Report. *J Pain Symptom Manage*. 2018 May;55(5):1321-6 e1. doi: 10.1016/j.jpainsymman.2018.01.018. PMID: 29421165. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
90. Luckett T, Phillips J, Johnson MJ, et al. Contributions of a hand-held fan to self-management of chronic breathlessness. *Eur Respir J*. 2017 Aug;50(2)doi: 10.1183/13993003.00262-2017. PMID: 28818884. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
91. Maeda T, Hayakawa T. Corticosteroids for alleviating dyspnea in patients with terminal cancer. *Progress in Palliative Care*. 2017;25(6):269-72. doi: 10.1080/09699260.2017.1392674. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
92. Mayrbaurl B, Giesinger JM, Burgstaller S, et al. Quality of life across chemotherapy lines in patients with advanced colorectal cancer: a prospective single-center observational study. *Support Care Cancer*. 2016 Feb;24(2):667-74. doi: 10.1007/s00520-015-2828-0. PMID: 26123602. **-Other: Not an included intervention**
93. Mercadante S, Casuccio A, Fulfaro F. The course of symptom frequency and intensity in advanced cancer patients followed at home. *J Pain Symptom Manage*. 2000 Aug;20(2):104-12. PMID: 10989248. **- Other: No intervention**
94. Mercadante S, Intravaia G, Villari P, et al. Controlled sedation for refractory symptoms in dying patients. *J Pain Symptom Manage*. 2009 May;37(5):771-9. doi: 10.1016/j.jpainsymman.2008.04.020. PMID: 19041216. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
95. Mercadante S, Porzio G, Valle A, et al. Palliative sedation in patients with advanced cancer followed at home: a prospective study. *J Pain Symptom Manage*. 2014 May;47(5):860-6. doi: 10.1016/j.jpainsymman.2013.06.019. PMID: 24099896. **- Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
96. Mercadante S, Villari P, David F, et al. Noninvasive ventilation for the treatment of dyspnea as a bridge from intensive to end-of-life care. *J Pain Symptom Manage*. 2009 Sep;38(3):e5-7. doi: 10.1016/j.jpainsymman.2009.04.016. PMID: 19559565. **-Case series or case reports**
97. Milbury K, Mallaiah S, Liao ZX, et al. Randomized controlled trial (RCT) of a dyadic yoga program for lung cancer patients undergoing radiotherapy and their family caregivers. *Journal of clinical oncology*. 2017;35(31):125-. doi: 10.1200/JCO.2017.35.31\_suppl.125. PMID: CN-01788582. **-No full report (e.g. conference or meeting abstract)**
98. Minchom A, Punwani R, Filshie J, et al. Anxiolytic effect of acupuncture in a phase II study of acupuncture and morphine for dyspnea in lung cancer and mesothelioma. *Journal of thoracic oncology*. 2017;12(1):S1415-S6. PMID: CN-01775113. **-No full report (e.g. conference or meeting abstract)**



99. Minchom AR, Punwani R, Filshie J, et al. A randomised study comparing the effectiveness of acupuncture (A) or morphine (M) versus the combination (AM) for the relief of dyspnoea in patients with advanced non small cell lung cancer and mesothelioma. Lung cancer (amsterdam, netherlands). 2016;91:S59-. PMID: CN-01437976. **-No full report (e.g. conference or meeting abstract)**
100. Nakano J, Fukushima T, Ishii S, et al. Effects of transcutaneous electrical nerve stimulation on pain and physical symptoms in patients with cancer: a pilot randomized crossover trial. Supportive care in cancer. 2018;26(2):S100-S1. doi: 10.1007/s00520-018-4193-2. PMID: CN-01605932. **-No full report (e.g. conference or meeting abstract)**
101. Nava S, Esquinas A, Ferrer M, et al. Multicenter randomized study of the use of non-invasive ventilation (NIV) vs oxygen therapy (O2) in reducing respiratory distress in end stage cancer patients. American thoracic society international conference, may 16-21, 2008, toronto. 2008:A767. PMID: CN-00679826. **-Other: Conference**
102. Navigante A, Sauri A, Palazzo F, et al. A randomised trial of subcutaneous (SC) morphine chloride (MC) and midazolam (M) vs oxygen (O2) therapy in patients (pts) with advanced cancer (AC) and severe dyspnea. Proceedings of the american society of clinical oncology. 1998;17:66a, Abstract 255. PMID: CN-00692227. **-Other: Conference**
103. Navigante A, Sauri A, Palazzo F, et al. Compared and randomized prospective trial between oxygenotherapy vs. morphine chloride + midazolam by subcutaneous route in patients with advanced cancer and dyspnea. Prensa Medica Argentina. 1997;84(5):474-6. **-Not in English**
104. Navigante AH, Cerchietti LCA, Cabalar ME. Morphine plus midazolam versus oxygen therapy on severe dyspnea management in the last week of life in hypoxemic advanced cancer patients. Medicina Paliativa. 2003;10(1):14-9. **-Not in English**
105. Nosedá A, Carpioux JP, Markstein C, et al. Disabling dyspnoea in patients with advanced disease: Tack of effect of nebulized morphine. European Respiratory Journal. 1997 May;10(5):1079-83. PMID: WOS:A1997WZ12500020. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
106. Nosek K, Leppert W, Nosek H, et al. A comparison of oral controlled-release morphine and oxycodone with transdermal formulations of buprenorphine and fentanyl in the treatment of severe pain in cancer patients. Drug Des Devel Ther. 2017;11:2409-19. doi: 10.2147/dddt.s141007. PMID: 28860712. **-Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
107. Odyne T, Briskin Y, Perederiy A, et al. Effect of water physical therapy on quality of life in breast cancer survivors. Physiotherapy Quarterly. 2018;26(4):11-6. doi: 10.5114/pq.2018.79741. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
108. Oh GH, Yeom CW, Shim EJ, et al. The effect of perceived social support on chemotherapy-related symptoms in patients with breast cancer: A prospective observational study. Journal of Psychosomatic Research. 2020;130doi: 10.1016/j.jpsychores.2019.109911. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
109. Puspawati N, Sitorus R, Herawati T. Hand-held Fan Airflow Stimulation Relieves Dyspnea in Lung Cancer Patients. Asia Pac J Oncol Nurs. 2017 Apr-Jun;4(2):162-7. doi: 10.4103/apjon.apjon\_14\_17. PMID: 28503650. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**



110. Quelch PC, Faulkner DE, Yun JW. Nebulized opioids in the treatment of dyspnea. *J Palliat Care*. 1997 Autumn;13(3):48-52. PMID: 9354041. - **Case series or case reports**
111. Quigley C, Joel S, Patel N, et al. A phase I/II study of nebulized morphine-6-glucuronide in patients with cancer-related breathlessness. *J Pain Symptom Manage*. 2002 Jan;23(1):7-9. PMID: 11779662. - **Study with less than ten patients in the main intervention group**
112. Ray AD, Williams BT, Mahoney MC. Respiratory muscle training improves exercise performance and quality of life in cancer survivors: A pilot study. *Rehabilitation Oncology*. 2017;35(2):81-9. doi: 10.1097/01.REO.0000000000000064. - **Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
113. Reuben DB, Mor V. Dyspnea in Terminally Ill Cancer-Patients. *Chest*. 1986 Feb;89(2):234-6. PMID: WOS:A1986AYU0600019. - **Other: No intervention**
114. Rietjens JA, van Zuylen L, van Veluw H, et al. Palliative sedation in a specialized unit for acute palliative care in a cancer hospital: comparing patients dying with and without palliative sedation. *J Pain Symptom Manage*. 2008 Sep;36(3):228-34. doi: 10.1016/j.jpainsymman.2007.10.014. PMID: 18411017. - **No patient reported outcomes and does not apply to harms KQ4**
115. Ríos BP, Villaverde RM, Martínez BMA, et al. Diagnostic protocol and treatment of dyspnea in cancer patient. *Medicine*. 2009;10(25):1704-6. doi: 10.1016/S0304-5412(09)70569-4. - **No original data (systematic reviews, meta-analysis, editorial, commentary)**
116. Rodriguez EJF, Galve MIR, Hernandez JJC. Effectiveness of an Occupational Therapy Program on Cancer Patients with Dyspnea: Randomized Trial. *Physical & Occupational Therapy in Geriatrics*. 2020;38(1):43-55. doi: 10.1080/02703181.2019.1683673. PMID: WOS:000495489200001. - **Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
117. Rosser R, Guz A. Psychological Approaches to Breathlessness and Its Treatment. *Journal of Psychosomatic Research*. 1981 1981;25(5):439-47. PMID: WOS:A1981MN76100026. - **No original data (systematic reviews, meta-analysis, editorial, commentary)**
118. Santiago TV, Johnson J, Riley DJ, et al. Effects of Morphine on Ventilatory Response to Exercise. *Journal of Applied Physiology*. 1979 1979;47(1):112-8. PMID: 468650. - **Study with less than ten patients in the main intervention group**
119. Schultheis CP. Nebulized fentanyl provides subjective improvements for patients with dyspnea. *Oncol Nurs Forum*. 2005 Jan;32(1):15; author reply doi: 10.1188/05.onf.15-16. PMID: 15682527. - **No full report (e.g. conference or meeting abstract)**
120. Schunk M, Dittmer J, Bausewein C. Replicability of complex interventions in randomized controlled trials: a case study of a breathlessness support service. *Palliative medicine*. 2018;32(1):141-2. doi: 10.1177/0269216318769196. PMID: CN-01606081. - **No full report (e.g. conference or meeting abstract)**
121. Sherwood P, Given BA, Given CW, et al. A cognitive behavioral intervention for symptom management in patients with advanced cancer. *Oncol Nurs Forum*. 2005 Nov;32(6):1190-8. PMID: WOS:000233574800013. - **Other: Combined symptom score, no separate dyspnea outcome**
122. Shima Y, Saito R. Alleviation of dyspnea in patients with advanced cancer: Usefulness of opioid; 1998. - **No full report (e.g. conference or meeting abstract)**



123. Sironi O, Sbanotto A, Banfi MG, et al. Midazolam as adjunct therapy to morphine to relieve dyspnea? J Pain Symptom Manage. 2007 Mar;33(3):233-4; author reply 4-6. doi: 10.1016/j.jpainsymman.2006.12.001. PMID: 17349490. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
124. Sitte T, Bausewein C. Intranasal fentanyl for episodic breathlessness. Journal of Pain and Symptom Management. 2008 2008-Dec;36(6):e3-6. PMID: 18954962. **-Case series or case reports**
125. Stein WM, Min YK. Nebulized morphine for paroxysmal cough and dyspnea in a nursing home resident with metastatic cancer. Am J Hosp Palliat Care. 1997 Mar-Apr;14(2):52-6. doi: 10.1177/104990919701400201. PMID: 9295402. **-No original data (systematic reviews, meta-analysis, editorial, commentary)**
126. Stone P, Kurowska A, Tookman A. Nebulized frusemide for dyspnoea. Palliat Med. 1994;8(3):258. doi: 10.1177/026921639400800315. PMID: 7952379. **-No full report (e.g. conference or meeting abstract)**
127. Su X, Li F, Zhao Q, et al. Quality of life levels and physical and mental states of dyspnoeic patients with advanced lung cancer effectively improved by comprehensive nursing intervention. International Journal of Clinical and Experimental Medicine. 2019;12(9):11700-7. **-No patient reported outcomes and does not apply to harms KQ4**
128. Tan SB, Liam CK, Pang YK, et al. The Effect of 20-Minute Mindful Breathing on the Rapid Reduction of Dyspnea at Rest in Patients With Lung Diseases: A Randomized Controlled Trial. J Pain Symptom Manage. 2019 Apr;57(4):802-8. doi: 10.1016/j.jpainsymman.2019.01.009. PMID: 30684635. **-Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
129. Tang WR, Yang SH, Yu CT, et al. Long-Term Effectiveness of Combined Treatment with Traditional Chinese Medicine and Western Medicine on the Prognosis of Patients with Lung Cancer. J Altern Complement Med. 2016 Mar;22(3):212-22. doi: 10.1089/acm.2015.0214. PMID: 26986673. **-Drug is not available in the U.S./ non-approved (e.g. Investigational)**
130. Ting FIL, Barbon CE, Estreller S, et al. The FAFA (FAn on FAcE) trial: A randomized clinical trial on the effect of a fan blowing air on the face to relieve dyspnea in Filipino patients with terminal cancer. Annals of Oncology. 2019 Nov;30 PMID: WOS:000503487700339. **-No full report (e.g. conference or meeting abstract)**
131. Vardy J, Bell ML, Van Der Ploeg HP, et al. The impact of physical activity on fatigue and quality of life in lung cancer patients: a randomized controlled trial (RCT). Journal of thoracic oncology. 2015;10(9):S363-. PMID: CN-01142700. **-No full report (e.g. conference or meeting abstract)**
132. Vardy JL, Bell M, Van Der Ploeg H, et al. The impact of physical activity on fatigue and quality of life in lung cancer patients: a randomised controlled trial (RCT). Journal of clinical oncology. 2015;33(15):CN-01098343. **-No full report (e.g. conference or meeting abstract)**
133. Walder D, Punwani R, Gunapala R, et al. Optimized inhaler therapy is superior to supportive care alone for dyspnea in patients with coexisting COPD and lung cancer. Journal of thoracic oncology. 2017;12(11):S2314-S5. PMID: CN-01451809. **-No full report (e.g. conference or meeting abstract)**
134. Wang TJ, Wang HM, Yang TS, et al. The effect of abdominal massage in reducing malignant ascites symptoms. Res Nurs Health. 2015 Feb;38(1):51-9. doi: 10.1002/nur.21637. PMID: 25558030. **-No patient reported outcomes and does not apply to harms KQ4**



135. Webb M, Moody LE, Mason LA. Dyspnea assessment and management in hospice patients with pulmonary disorders. *Am J Hosp Palliat Care*. 2000 Jul-Aug;17(4):259-64. doi: 10.1177/104990910001700412. PMID: 11883802. - **Addresses effectiveness KQs (1-3) BUT NOT a RCT, nonrandomized controlled trial, cross over trial, and observational studies with a concurrent comparison group**
136. Wiggeraad F, Bolam KA, Mijwel S, et al. Long-Term Favorable Effects of Physical Exercise on Burdensome Symptoms in the OptiTrain Breast Cancer Randomized Controlled Trial. *Integrative Cancer Therapies*. 2020;19doi: 10.1177/1534735420905003. - **Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
137. Winning AJ, Hamilton RD, Shea SA, et al. The Effect of Airway Anesthesia on the Control of Breathing and the Sensation of Breathlessness in Man. *Clinical Science*. 1985 1985;68(2):215-25. PMID: 3917883. - **Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
138. Wróblewska I, Turek R, Sochocka L, et al. Quality of life of patients undergoing long-term oxygen therapy. *Family Medicine and Primary Care Review*. 2011;13(3):542-6. - **Not in English**
139. Yamaguchi T, Matsuda Y, Matsuoka H, et al. Efficacy of immediate-release oxycodone for dyspnoea in cancer patient: cancer dyspnoea relief (CDR) trial. *Japanese journal of clinical oncology*. 2018;48(12):1070-5. doi: 10.1093/jjco/hyy139. PMID: CN-01667169. - **Study with less than ten patients in the main intervention group**
140. Yang G, Tan D, Neo S, et al. Pilot randomized phase II trial of the enhancing quality of life in patients (EQUIP) intervention for patients with advanced lung cancer. *Palliative medicine*. 2018;32(1):92-3. doi: 10.1177/0269216318769196. PMID: CN-01606042. - **No full report (e.g. conference or meeting abstract)**
141. Yang GM, Teo I, Neo SH, et al. Pilot Randomized Phase II Trial of the Enhancing Quality of Life in Patients (EQUIP) Intervention for Patients With Advanced Lung Cancer. *Am J Hosp Palliat Care*. 2018 Aug;35(8):1050-6. doi: 10.1177/1049909118756095. PMID: 29409327. - **No patient reported outcomes and does not apply to harms KQ4**
142. Yao J, Liang Y, Jiang M, et al. Effects of psychological nursing intervention on pain and adverse psychology in patients with lung cancer. *International Journal of Clinical and Experimental Medicine*. 2019;12(11):12808-16. - **Intent of the intervention is NOT to alleviate dyspnea**
143. Yates P, Hardy J, Kwun F, et al. A randomised controlled trial of a nonpharmacological intervention for dyspnoea. *Asia-pacific journal of clinical oncology*. 2011;7:82-. doi: 10.1111/j.1743-7563.2011.01477.x. PMID: CN-01003538. - **No full report (e.g. conference or meeting abstract)**
144. Yennurajalingam S, Williams JL, Chisholm G, et al. Effects of Dexamethasone and Placebo on Symptom Clusters in Advanced Cancer Patients: A Preliminary Report. *Oncologist*. 2016 Mar;21(3):384-90. doi: 10.1634/theoncologist.2014-0260. PMID: 26888692. - **No patient reported outcomes and does not apply to harms KQ4**
145. Yilmaz S, Yaka E, Yuksel M, et al. Nonopioid therapy for cancer related dyspnea palliation in the ED: A randomized double blind clinical trial. *Acta Medica Mediterranea*. 2017;2017(6):1099-106. - **Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**
146. Zhang C, Guo H, Shen M, et al. Comparison of clinical effectiveness of nurse led care among Chinese patients with cancer: A prospective study evaluating effective patient care compared to consultant oncologist. *J Infect Public Health*. 2019 Aug 3doi: 10.1016/j.jiph.2019.07.010. PMID: 31387796. - **Not evaluating Patients (≥18 years of age) with advanced cancer (unlikely to be cured or unlikely to be controlled with treatment) and dyspnea**



147. Zimmermann C, Hannon B, Krzyzanowska MK, et al. Phase 2 trial of Symptom screening with Targeted Early Palliative care (STEP) for patients with advanced cancer. *Journal of clinical oncology*. 2019;37doi: 10.1200/JCO.2019.37.15\_suppl.11604. PMID: CN-01986677. **-No full report (e.g. conference or meeting abstract)**

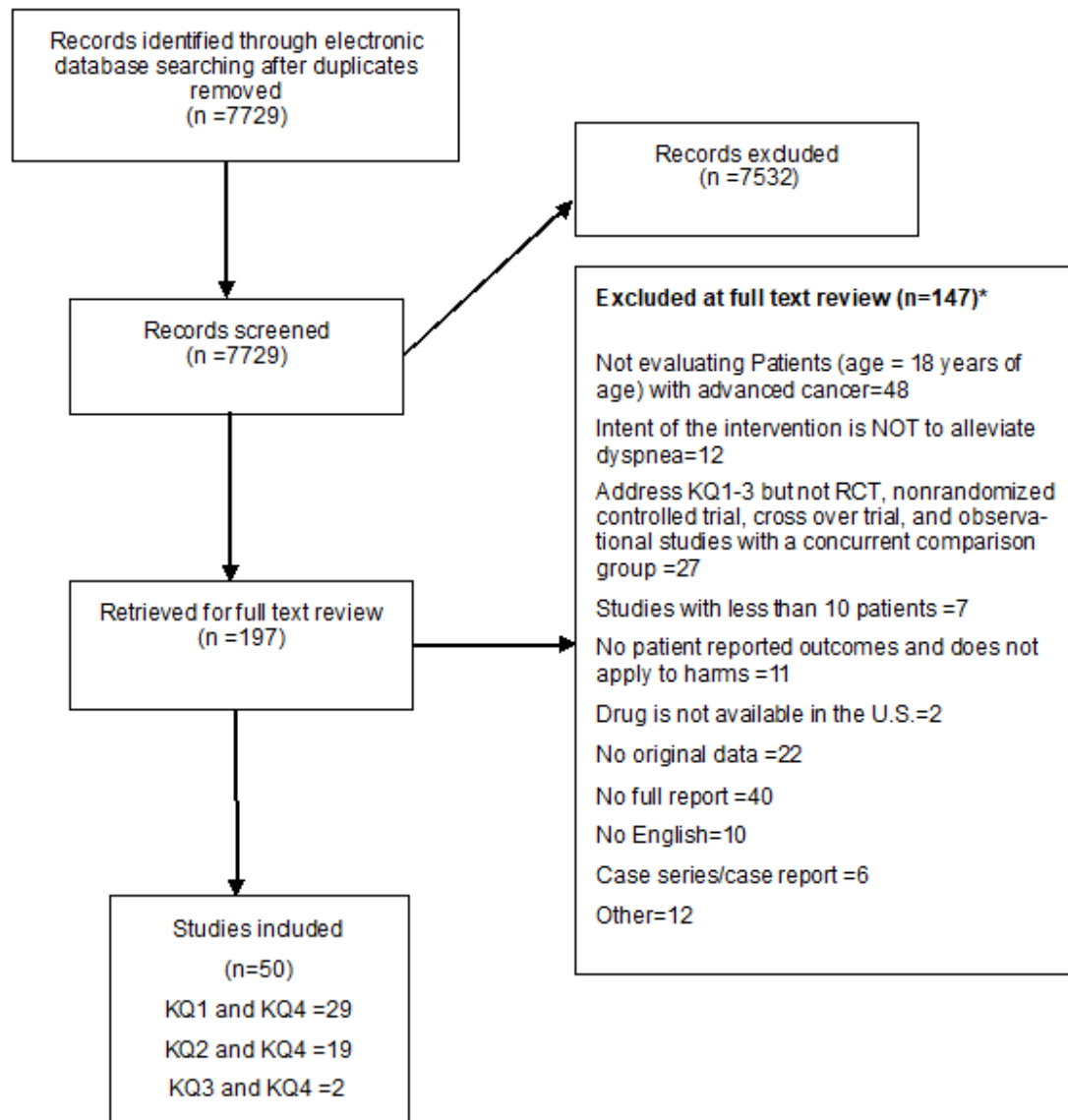


## Appendix C. Results

### Search Results

We retrieved 7172 unique citations (Figure C-1). After screening abstracts and full-text, we included 41 studies. Appendix B provides a list of the excluded articles at full-text screen.

**Figure C-1. Summary of the literature search**



\* Total exceeds the number of citations in the exclusion box, because citations could be excluded for more than



## **Characteristics of Included Studies**

Additional details of included studies are found in Appendix D: Evidence Tables. These include study characteristics, inclusion and exclusion criteria, participant characteristics, intervention details, and all relevant outcomes.



## Included Studies

1. Aabom B, Laier G, Christensen PL, et al. Oral morphine drops for prompt relief of breathlessness in patients with advanced cancer-a randomized, double blinded, crossover trial of morphine sulfate oral drops vs. morphine hydrochloride drops with ethanol (red morphine drops). *Support Care Cancer*. 2019 Dec 2doi: 10.1007/s00520-019-05116-1. PMID: 31792878.
2. Allard P, Lamontagne C, Bernard P, et al. How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial. *J Pain Symptom Manage*. 1999 Apr;17(4):256-65. PMID: 10203878.
3. Booth S, Kelly MJ, Cox NP, et al. Does oxygen help dyspnea in patients with cancer? *Am J Respir Crit Care Med*. 1996 May;153(5):1515-8. doi: 10.1164/ajrccm.153.5.8630595. PMID: 8630595.
4. Bordeleau L, Szalai JP, Ennis M, et al. Quality of life in a randomized trial of group psychosocial support in metastatic breast cancer: overall effects of the intervention and an exploration of missing data. *J Clin Oncol*. 2003 May 15;21(10):1944-51. doi: 10.1200/jco.2003.04.080. PMID: 12743147.
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**Table C-1. Summary of findings for the effects of pharmacological interventions on clinical utilization health outcomes in patients with advanced cancer**

Outcome	Comparison	Number of Studies Reporting Outcome (N analyzed)	Findings	Conclusion
<b>Blood pressure</b>	Opioid vs. placebo	<b>2 RCTs</b>	Pooled analysis:	<ul style="list-style-type: none"> <li>• There was no difference between opioids and placebo in the effect on blood pressure</li> </ul>
	Fentanyl vs. placebo (2)	(N=44)	<ul style="list-style-type: none"> <li>• Diastolic, SMD: 0.243; 95% CI, -0.23 to 1.41</li> <li>• Systolic, SMD: 0.478; 95% CI, -0.13 to 1.09</li> </ul>	
	Opioid vs. opioid	<b>1 RCTs</b>	<ul style="list-style-type: none"> <li>• Diastolic, difference between beginning and end of walk, calculated SMD: 0.14; 95% CI, -0.54 to 0.81</li> <li>• Systolic, difference between beginning and end of walk, calculated SMD: 0.17; 95% CI, -0.51 to 0.84</li> </ul>	<ul style="list-style-type: none"> <li>• There was no significant change in blood pressure in patients in either arm</li> </ul>
<b>Heart rate</b>	Opioids vs. placebo	<b>3 RCTs</b>	Pooled analysis with Charles, 2008 et al. <sup>1</sup> saline vs. nebulized hydromorphone comparison:	<ul style="list-style-type: none"> <li>• There was no significant difference between opioids and placebo in the effect on heart rate.</li> </ul>
	Fentanyl vs. placebo (2) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)	(N=64)	<ul style="list-style-type: none"> <li>• SMD: -0.14 (95% CI: -0.57 to 0.29),</li> <li>• I-squared=0.0%, p=0.66</li> </ul> <p>Pooled analysis with Charles, 2008 et al.<sup>1</sup> saline vs. systemic hydromorphone comparison:</p> <ul style="list-style-type: none"> <li>• SMD: -0.03 (95% CI: -0.46 to 0.4)</li> <li>• I-squared=0.0%, p=0.46</li> </ul>	
	Opioid vs. opioid	<b>3 RCTs</b>	Pooled analysis:	<ul style="list-style-type: none"> <li>• There was no significant difference between opioids in the effect on heart rate</li> </ul>
	sublingual vs. subcutaneous morphine (1) High dose vs. low dose fentanyl (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)	(N=70)	<ul style="list-style-type: none"> <li>• SMD: 0.11; 95% CI, -0.3 to 0.52</li> <li>• I-squared=0.0%, p=0.79</li> </ul>	



Outcome	Comparison	Number of Studies Reporting Outcome (N analyzed)	Findings	Conclusion
<b>Oxygen saturation</b>	Opioid vs. placebo  Fentanyl vs. placebo (4) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1) Morphine vs. placebo (1)	<b>6 RCTs</b>  (N=107)	Pooled analysis with Charles, 2008 et al. <sup>1</sup> saline vs. nebulized hydromorphone comparison: <ul style="list-style-type: none"> <li>• SMD: -0.07 (95% CI: -0.40 to 0.25),</li> <li>• I-squared=0.0%, p=0.65</li> </ul> Pooled analysis with Charles, 2008 et al. <sup>1</sup> saline vs. systemic hydromorphone comparison: <ul style="list-style-type: none"> <li>• SMD: -0.13 (95% CI: -0.45 to 0.19)</li> <li>• I-squared=0.0%, p=0.63</li> </ul>	<ul style="list-style-type: none"> <li>• There was no difference between opioids and placebo in the effect on oxygen saturation.</li> </ul>
	Opioid vs. opioid  Fentanyl vs. morphine (1) High dose vs. low dose fentanyl (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)	<b>3 RCTs</b>  (N=62)	Pooled analysis: <ul style="list-style-type: none"> <li>• SMD: -0.03; 95% CI, -0.44 to 0.37</li> <li>• I-squared=0.0%, p=0.60</li> </ul>	<ul style="list-style-type: none"> <li>• There was no difference in the effect on oxygen saturation between opioids.</li> </ul>
	Opioid vs. anxiolytics  Oral morphine vs. oral midazolam (1) Subcutaneous morphine vs. subcutaneous midazolam vs. combination (1)	<b>2 RCTs</b>  (N=133)	90 minutes (calculated SMD: 0.001, 95% CI, -0.49 to 0.5) or Day 5 (calculated SMD: -0.003, 95% CI, -0.5 to 0.49)  Second study reported no significant differences between groups. Unable to calculate SMD, no variability reported	<ul style="list-style-type: none"> <li>• There was no difference in the effect on oxygen saturation for opioids compared to anxiolytics</li> </ul>



Outcome	Comparison	Number of Studies Reporting Outcome (N analyzed)	Findings	Conclusion
<b>Respiratory rate</b>	Opioid vs. placebo  Fentanyl vs. placebo (3) Hydromorphone (nebulized) vs. hydromorphone (Oral or subcutaneous) vs. placebo (nebulized) (1) Morphine vs. placebo (1)	<b>5 RCTs</b>  (N=94)	Pooled analysis with Charles, 2008 et al. <sup>1</sup> saline vs. nebulized hydromorphone comparison: <ul style="list-style-type: none"> <li>SMD: 0.11 (95% CI: -0.25 to 0.47),</li> <li>I-squared=0.0%, p=0.44</li> </ul> Pooled analysis with Charles, 2008 et al. <sup>1</sup> saline vs. systemic hydromorphone comparison: <ul style="list-style-type: none"> <li>SMD: 0.05 (95% CI: -0.31 to 0.41)</li> <li>I-squared=1.0%, p=0.40</li> </ul>	<ul style="list-style-type: none"> <li>There was no difference between opioids and placebo in the effect on respiratory rate.</li> </ul>
	Opioid vs. opioid  Low dose vs. high dose opioid (drug unspecified) (1) Morphine vs. fentanyl (1) High dose vs. low dose fentanyl (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)	<b>4 RCTs</b>  (N=89)	Pooled analysis: <ul style="list-style-type: none"> <li>SMD: -0.23 (95% CI, -0.63 to 0.18)</li> <li>I-squared=0.0%, p=0.91</li> </ul>	<ul style="list-style-type: none"> <li>There was no difference between opioids in the effect on respiratory rate</li> </ul>

SMD: standardized mean difference, RR: relative risk, MBGD: mean between group difference; vs= versus



**Table C-2. KQ4 -Rate of dropouts associated with nonpharmacological interventions in patients with advanced cancer**

<b>Intervention</b>	<b>Author, Year</b>	<b>Time of Assessing Attrition</b>	<b>Not Completing Last Followup (Attrition) N (%)</b>	<b>Attrition Due To Death or Clinical Deterioration, N (%)</b>	<b>Attrition Due To True Dropout (Loss to Followup or Adverse Event), N (%)</b>	<b>Reasons/Comments</b>
<b>Activity and rehabilitation</b>	Molassiotis, 2017 <sup>2</sup>	12 weeks	11/ 47 (23%), 5/23 (22%) in control and 6/24 (25%) in intervention arm.	11/ 47 (23%)	None	All attrition due to death/ clinical deterioration
	Hwang, 2012 <sup>3</sup>	8 weeks	6/ 24 (25%)	3/24 (12.5%) due to change in treatment	3/24 (12.5%) due to personal reasons	Mix of death/ clinical deterioration and loss to follow- up
	Henke, 2014 <sup>4</sup>	9 weeks	15/ 44 (34%)	7/44 (16%)	8/44 (18%), 7/20 (35%) in control arm, 1/24 (4%) in intervention arm.	Mix of death/ clinical deterioration and loss to follow- up
	Vanderbyl, 2017 <sup>5</sup>	6 weeks	12/ 36 (33%), 8/19 (42%) in qigong arm, 4/17 (24%) in exercise arm	NR	NR	Cause of attrition not reported. After crossover (6 more weeks), attrition increased to 17/ 36 (46%)
	Rutkowski, 2019 <sup>6</sup>	6 weeks	2/20 (10%) in intervention arm, 1/10 (10%) in control arm	3/30 (10%)	None	All dropouts related to death or clinical deterioration.
	Ligibel, 2016 <sup>7</sup>	16 weeks	15/48 (31%) in intervention arm, 10/ 53 (19%) in control arm.	6/101 (6%)	24/ 101 (24%)	Several patients unreachable by study team.
<b>Behavioral/ psychoeducational</b>	Bordeleau, 2003 <sup>8</sup>	12 months	144/215 (67%), 52/70 (74%) in control and 92/145 (63%) in intervention arm	NR	NR	Overall rate of death in arms was high but exact numbers not reported, most attrition likely to be death
	McMillan, 2007 <sup>9</sup>	30 days	227/329 (69%), rate similar across arms (64%-72%)	NR	NR	Overall rate of death in arms was high but exact numbers not reported, most attrition likely to be death
	Moore, 2012 <sup>10</sup>	3 months	47/ 202 (23%)	40/202 (20%)	7/ 202 (4%), 1/102 (1%) in control arm, 6/99 (6%) in intervention arm	Mix of death/ clinical deterioration and loss to follow- up. Attrition also reported at longer follow-up of 12 months, 70%



<b>Intervention</b>	<b>Author, Year</b>	<b>Time of Assessing Attrition</b>	<b>Not Completing Last Followup (Attrition) N (%)</b>	<b>Attrition Due To Death or Clinical Deterioration, N (%)</b>	<b>Attrition Due To True Dropout (Loss to Followup or Adverse Event), N (%)</b>	<b>Reasons/Comments</b>
<b>Integrative medicine</b>	Wyatt, 2012 <sup>11</sup>	11 weeks	85/286 (30%), 33/96, (35%) in usual care arm, 28/ 95 (29%) in sham arm, and 24/96 (25%) in intervention arm	NR	NR	Cause of attrition not reported.
	Vickers, 2005 <sup>12</sup>	1 week	1/ 46 (2%), 1/21 (5%) in control arm, 0/25 (0%) in intervention arm	None	1/ 46 (2%)	N=1, loss to follow up
	Dogan, 2019 <sup>13</sup>	4 weeks	16/ 76 (21%), 7/38 (18%) in control arm, 9/38 (21%) in intervention arm	5/ 76 (7%), 2/38 in control arm (5%), 3/ 38 (8%) in intervention arm	11/ 76 (15%), 5/38 (13%) in control arm and 6/38 (16%) in intervention arm.	Reason for attrition included 2/38 (5%) in intervention arm due to local symptoms (sensitivity, ecchymosis, pain in region of acupressure).
<b>Respiratory</b>	Hui, 2013 <sup>14</sup>	2 hours	7/30 (23%), 2/15 (13%) in high flow nasal cannula arm, and 5/15 (33%) in bilevel ventilation arm	NR	NR	Exact cause not reported but likely to be intolerance
	Nava, 2013 <sup>15</sup>	48 hours	11/99 (11%) in bilevel ventilation arm, 0/101 in oxygen arm, (0%), overall 11/ 200 (5.5%)	None	11/99, (11%) in bilevel ventilation arm	N=11, anxiety/ intolerance
	Bruera, 2003 <sup>16</sup>	11 minutes	1/34, 3%	None	1/34, 3%	N=1, time constraints



<b>Intervention</b>	<b>Author, Year</b>	<b>Time of Assessing Attrition</b>	<b>Not Completing Last Followup (Attrition) N (%)</b>	<b>Attrition Due To Death or Clinical Deterioration, N (%)</b>	<b>Attrition Due To True Dropout (Loss to Followup Or Adverse Event), N (%)</b>	<b>Reasons/Comments</b>
<b>Activity and rehabilitation and behavioral/ psychoeducational</b>	Corner, 1996 <sup>17</sup>	12 weeks	14/ 34 (41%), 6/15 (40%) in control arm, 8/19 (42%) in intervention arm.	14/ 34 (41%)	None	All attrition due to death/ clinical deterioration
	Chan, 2011 <sup>18</sup>	12 weeks	38/ 140 (27%), 30/70 (42%) in control arm, and 8/70 (11%) in intervention arm	38/ 140 (27%)	None	All attrition due to death/ clinical deterioration. Attrition was progressive: 4% at 3 weeks, 9% at 6 weeks, and 27% at 12 weeks.
	Dhillon, 2017 <sup>19</sup>	2 months	21/ 111 (19%) overall, 8/56 (14%) in intervention arm, 13/55 (24%) in control arm	16/111 (14%)	5/111 (5%) at 2 months	Attrition increased from 19% at 2 months to 56% at 6 months
<b>Behavioral/ psychoeducational and integrative medicine</b>	Mosher, 2019 <sup>20</sup>	6 weeks	12/50 (24%), 7/25 (35%) in control arm, 5/25 (25%) in intervention arm.	10/ 50 (20%)	2/50 (4%), 1/25 (4%) in control arm, 1/25 (4%) in intervention arm.	N=2 of attrition due to lack of interest
<b>Activity and rehabilitation and Behavioral/ psychoeducational and integrative medicine</b>	Farquhar, 639 <sup>21</sup>	2 weeks	13/ 67 (19%), 6/32 (19%) in control arm, 7/35 (20%) in intervention arm.	13/ 67 (19%),	None	All attrition due to death/ clinical deterioration
	Yorke, 2015 <sup>22</sup>	12 weeks	30/101 (30%), 19/50 (38%) in control arm, 11/51 (22%) in intervention arm	12/ 101 (12%)	18/101 (18%)	Mix of death/ clinical deterioration and loss to follow-up.



**Table C-3. KQ4--List of studies reporting harms and dropouts in studies of pharmacological interventions for breathlessness in patients with advanced cancer**

Intervention	Author, Year	N	Central Nervous System	Gastro-intestinal	Pruritus	Urinary Retention	Dry Mouth	Dropouts
<b>Opioids vs. Placebo</b>	Hui, 2017 <sup>23</sup>	● 20	X	X	X			X
	Hui, 2016 <sup>24</sup>	● 24	X	X				
	Hui, 2014 <sup>25</sup>	● 20	X	X	X			
	Pinna, 2015 <sup>26</sup>	● 13		X				
	Charles, 2008 <sup>1</sup>	● 20						X
<b>Anxiolytics vs. Placebo</b>	Peoples, 2016 <sup>27</sup>	● 379						X
	Hardy, 2016 <sup>28</sup>	● 73	X					
<b>Placebo vs. Corticosteroids vs. Placebo</b>	Hui, 2016 <sup>29</sup>	● 41	X	X				X
<b>Opioids vs. Opioids</b>	Kawabata, 2013 <sup>30</sup>	● 95	X	X	X	X		
	Bruera, 2005 <sup>31</sup>	● 12	X	X				
	Hui, 2019 <sup>32</sup>	● 30	X	X	X			
<b>Opioids vs. Anxiolytics</b>	Navigante, 2010 <sup>33</sup>	● 63	X	X	X		X	X
<b>Opioids vs. Anxiolytics vs. Combination</b>	Navigane, 2006 <sup>34</sup>	● 101	X	X			X	
<b>Opioids vs. Corticosteroids vs. Bronchodilators</b>	Tian, 2016 <sup>35</sup>	● 343	X	X			X	

N=sample size



**Table C-4. Summary of the strength of evidence for the key outcomes**

Key Outcome	Improvement [Favor intervention]	Equivalence [No difference]	No Conclusion [Insufficient evidence]
<b>Breathlessness</b>	<p><b><u>Moderate strength of evidence</u></b></p> <ul style="list-style-type: none"> <li>Airflow vs usual care/ placebo [3 RCTs (115); SMD, -2.09 (95% CI, -3.81 to -0.37)]</li> </ul> <p><b><u>Low strength of evidence</u></b></p> <ul style="list-style-type: none"> <li>Bilevel ventilation vs standard supplemental oxygen [1 RCT (189)]</li> <li>Acupressure/ reflexology vs. sham intervention or usual care or both [2 RCTs (206)]</li> <li>Combined behavioral/psychoeducational, activity/ rehabilitation and integrative medicine interventions, vs. usual care [2 RCTs (100); mean between group difference 5.19 (95% CI, 0.62 to 9.75), and -1.29 (95% CI, -2.57 to -0.005)]</li> </ul>	<p><b><u>Moderate strength of evidence</u></b></p> <ul style="list-style-type: none"> <li>Opioids vs Placebo [6 RCT (107)]</li> </ul> <p><b><u>Low strength of evidence</u></b></p> <ul style="list-style-type: none"> <li>Compressed air vs oxygen [4 RCTs (96)]</li> <li>Bilevel ventilation vs high flow nasal cannula [1 RCT (30)]</li> <li>Behavioral and psychoeducational interventions vs usual care [3 RCTs (197)]</li> <li>Activity and rehabilitation interventions vs activity and rehabilitation interventions or usual care [7 RCTs (227)]</li> <li>Combined Activity and Rehabilitation and Behavioral Psychoeducational Interventions, vs usual care [3 RCTs (184)]</li> <li>Anxiolytics vs Placebo [2 RCT (311)]</li> <li>Opioids vs Opioids [7 RCT (132)]</li> <li>Opioids vs Anxiolytics [2 RCT (108)]</li> </ul>	<ul style="list-style-type: none"> <li>Acupuncture vs sham acupuncture [1 RCT (33)]</li> <li>Music therapy vs usual care [1 RCT (40)]</li> <li>Combined behavioral/ psychoeducational and integrative medicine interventions vs. usual care [1 RCT (38)]</li> <li>Corticosteroids vs Placebo [1 RCT (28)]</li> <li>Opioids vs Corticosteroids vs Bronchodilators [1 retrospective cohort (343)]</li> <li>Opioids vs acupuncture vs Opioid-acupuncture combinations [1 RCT (145)]</li> <li>Multimodal management of chronic obstructive pulmonary disease vs usual care [1 RCT (77)]</li> </ul>



Key Outcome	Improvement [Favor intervention]	Equivalence [No difference]	No Conclusion [Insufficient evidence]
Anxiety		<u>Low strength of evidence</u> <ul style="list-style-type: none"> <li>• Combined behavioral/ psychoeducational and activity/ rehabilitation Interventions vs. usual care [3 RCTs (212)]</li> <li>• Combined behavioral/ psychoeducational, activity/ rehabilitation and integrative medicine Interventions vs. usual care [2 RCTs (99)]</li> <li>• Anxiolytics vs Placebo [2 RCT (311)]</li> </ul>	<ul style="list-style-type: none"> <li>• Airflow vs. usual care or sham [1 RCT (40)]</li> <li>• Activity and rehabilitation interventions vs activity and rehabilitation interventions or usual care [2 RCTs (60)]</li> <li>• Acupressure/ reflexology vs. sham intervention or usual care or both [1 RCT (222)]</li> <li>• Music therapy vs control group[1 RCT (40)]</li> <li>• Combined Behavioral/ Psychoeducational and Integrative Medicine Interventions vs. usual care [1 RCT (38)]</li> <li>• Opioids vs acupuncture vs Opioid-acupuncture combinations [1 RCT (145)]</li> </ul>
Exercise capacity	<u>Low strength of evidence</u> <ul style="list-style-type: none"> <li>• Activity/ rehabilitation interventions vs. activity/ rehabilitation interventions or usual care [3 RCTs (72)]</li> </ul>	<u>Moderate strength of evidence</u> <ul style="list-style-type: none"> <li>• Opioids vs Placebo [3 RCT (57)]</li> </ul>	<ul style="list-style-type: none"> <li>• Compressed air vs standard supplemental oxygen [1 RCT (33)]</li> <li>• Acupressure/ reflexology vs. sham intervention or usual care or both [1 RCT (60)]</li> <li>• Combined behavioral/ psychoeducational and activity/ rehabilitation Interventions vs. usual care [1 RCT(62)]</li> <li>• Opioids vs acupuncture vs combination</li> </ul>



Key Outcome	Improvement [Favor intervention]	Equivalence [No difference]	No Conclusion [Insufficient evidence]
Health-related quality of life		<p><b><u>Low strength of evidence</u></b></p> <ul style="list-style-type: none"> <li>• Acupressure/ reflexology vs. sham intervention or usual care or both [2 RCTs (206); -2.00 (95% CI; -5.76 to 1.76)]</li> <li>• Behavioral and psychoeducational interventions vs usual care [3 RCTs (197)]</li> <li>• Activity and rehabilitation interventions vs activity and rehabilitation interventions or usual care [5 RCTs (188)]</li> <li>• Combined behavioral/psychoeducational, activity/ rehabilitation, and integrative medicine interventions vs. usual care [2 RCTs (99)]</li> </ul>	<ul style="list-style-type: none"> <li>• Combined behavioral/ psychoeducational and activity/ rehabilitation Interventions vs. usual care [1 RCT (62)]</li> <li>• Corticosteroids vs Placebo [1 RCT (28)]</li> <li>• Opioids vs acupuncture vs Opioid-acupuncture combinations [1 RCT (145)]</li> <li>• Multimodal management of chronic obstructive pulmonary disease vs usual care [1 RCT (74)]</li> </ul>

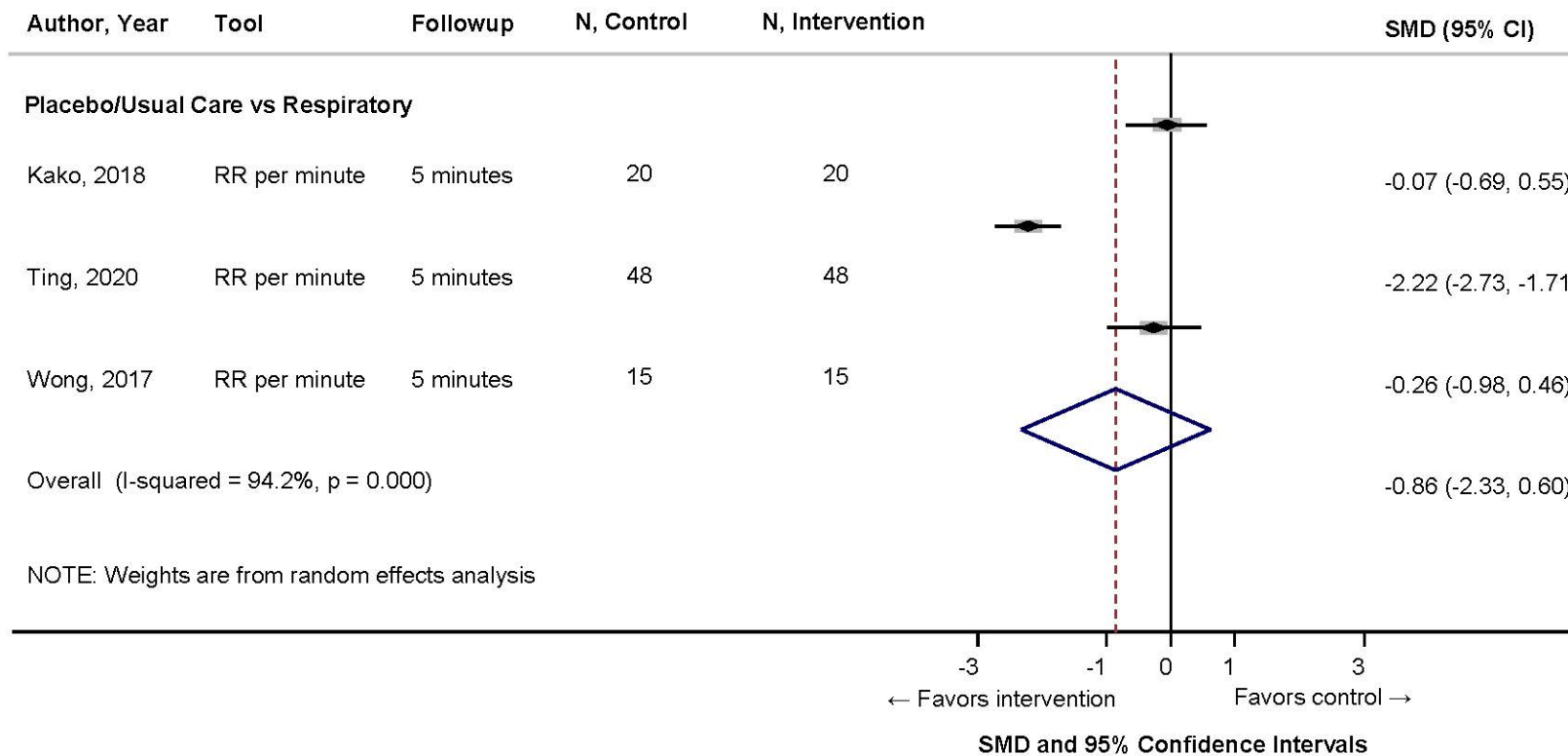
CI=confidence intervals; N=population available for analysis; RCT=randomized clinical trial; SMD=standardized mean difference



## Meta-Analysis Figures

### Key Question 1: Meta-Analysis of Nonpharmacological Interventions

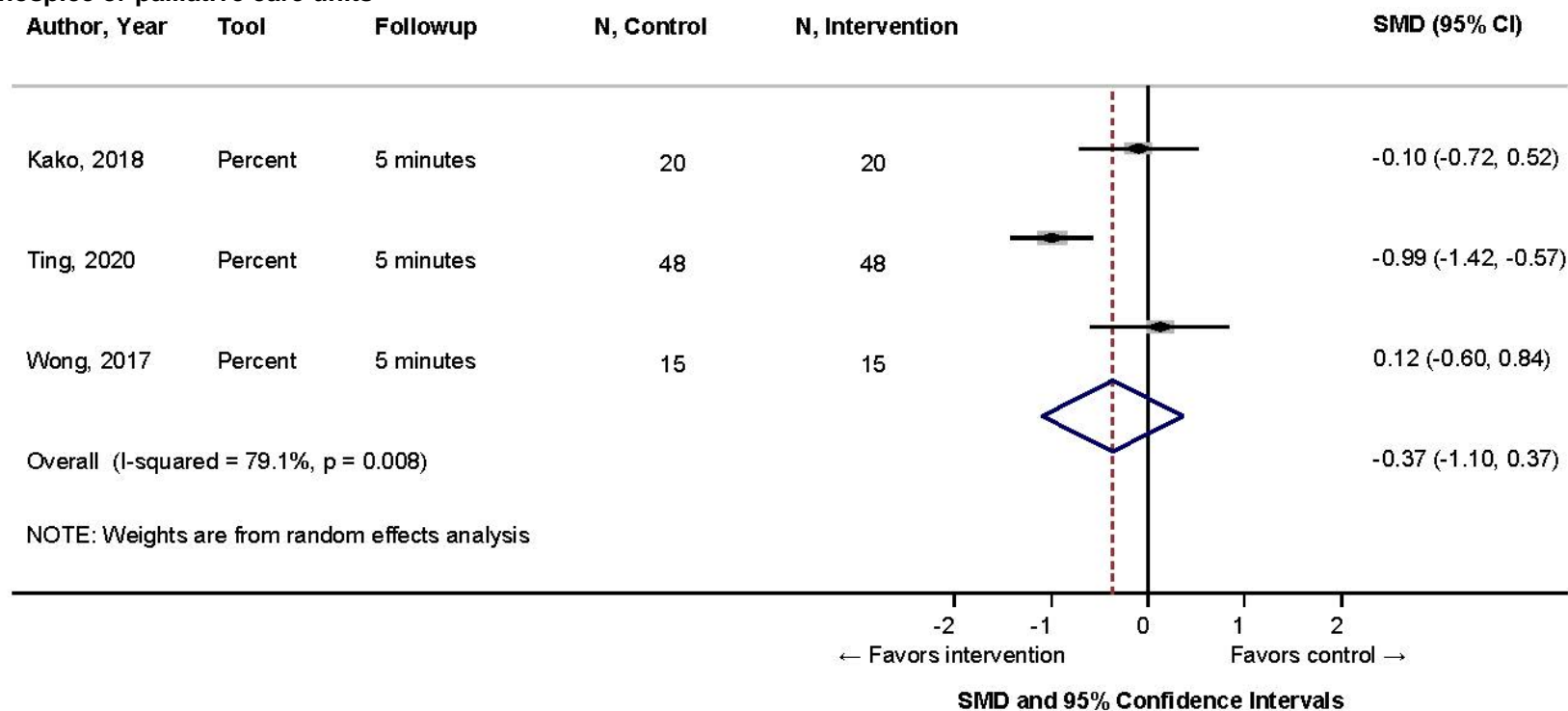
**Figure C-2. Meta-analysis of the effects of airflow interventions on respiratory rate in patients with advanced cancer in inpatient hospice or palliative care units**



CI=confidence interval; N=sample size; RR=respiratory rate; SMD=standardized mean difference



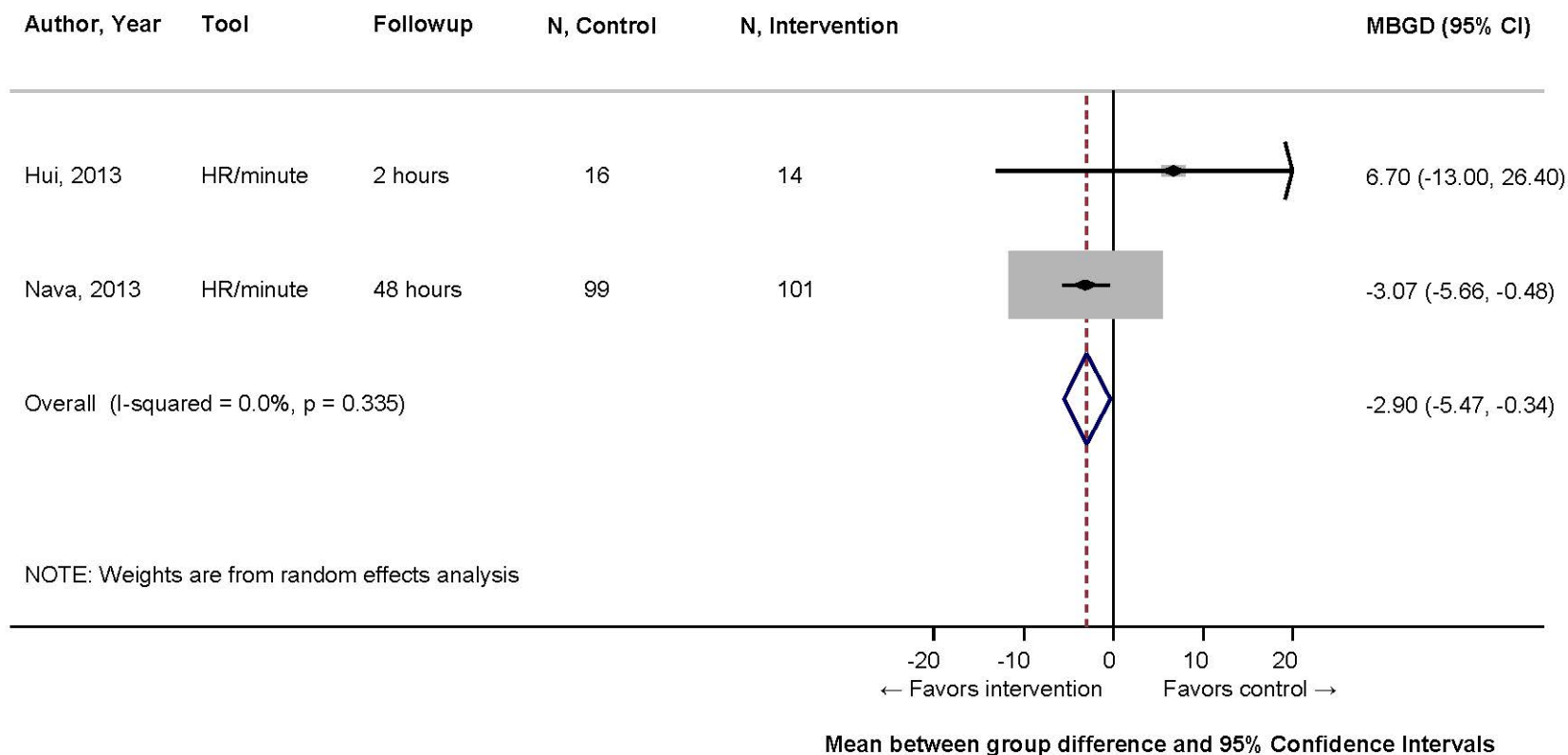
**Figure C-3. Meta-analysis of the effects of airflow interventions on oxygen saturation in patients with advanced cancer in inpatient hospice or palliative care units**



CI=confidence interval; N=sample size; SMD=standardized mean difference



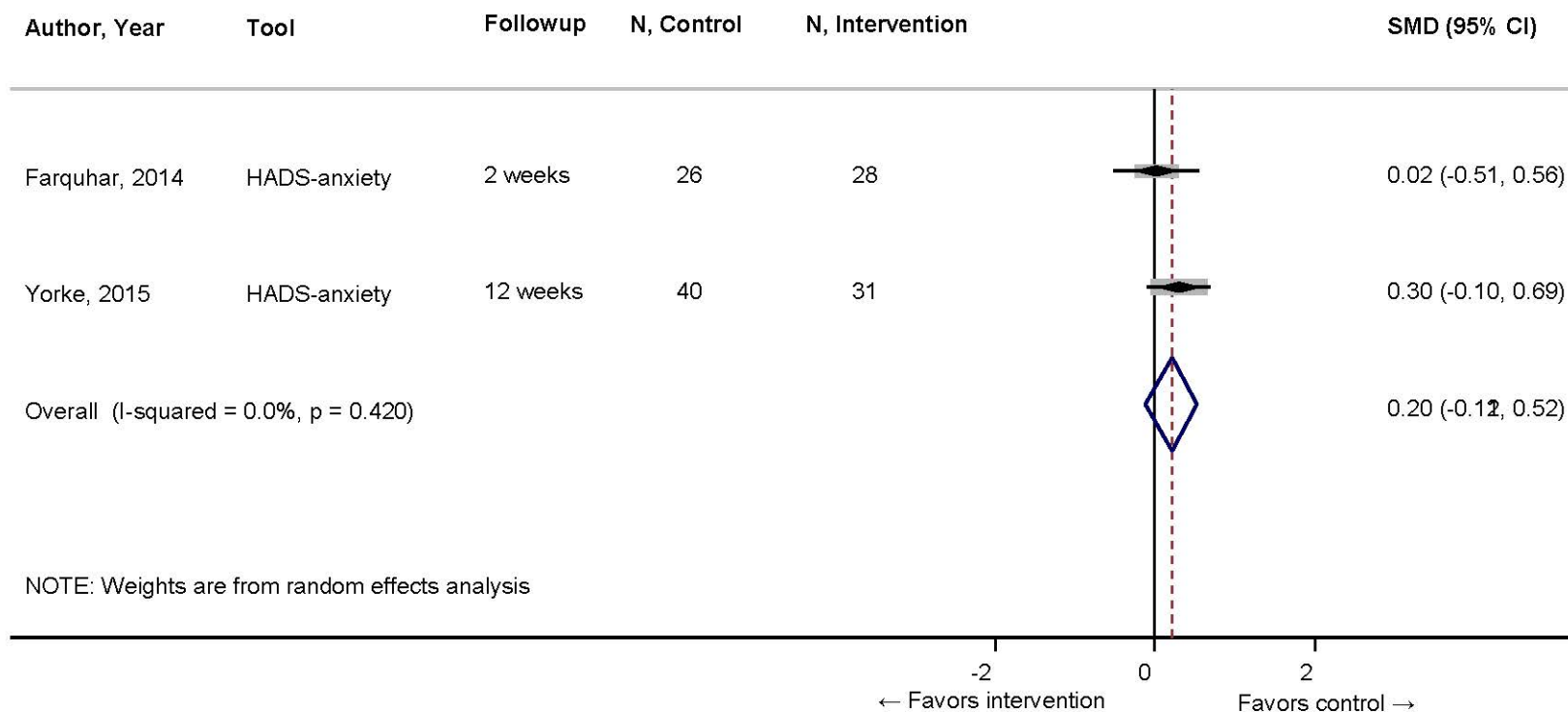
**Figure C-4. Meta-analysis of the effects of bilevel ventilation interventions on heart rate in patients with advanced cancer in inpatient hospice or palliative care units**



CI=confidence interval; HR=heart rate; N=sample size; SMD=standardized mean difference



**Figure C-5. Meta-analysis of the effects of combined activity/rehabilitation, behavioral/psychoeducational, and integrative medicine interventions on anxiety in patients with advanced cancer in inpatient hospice or palliative care units**

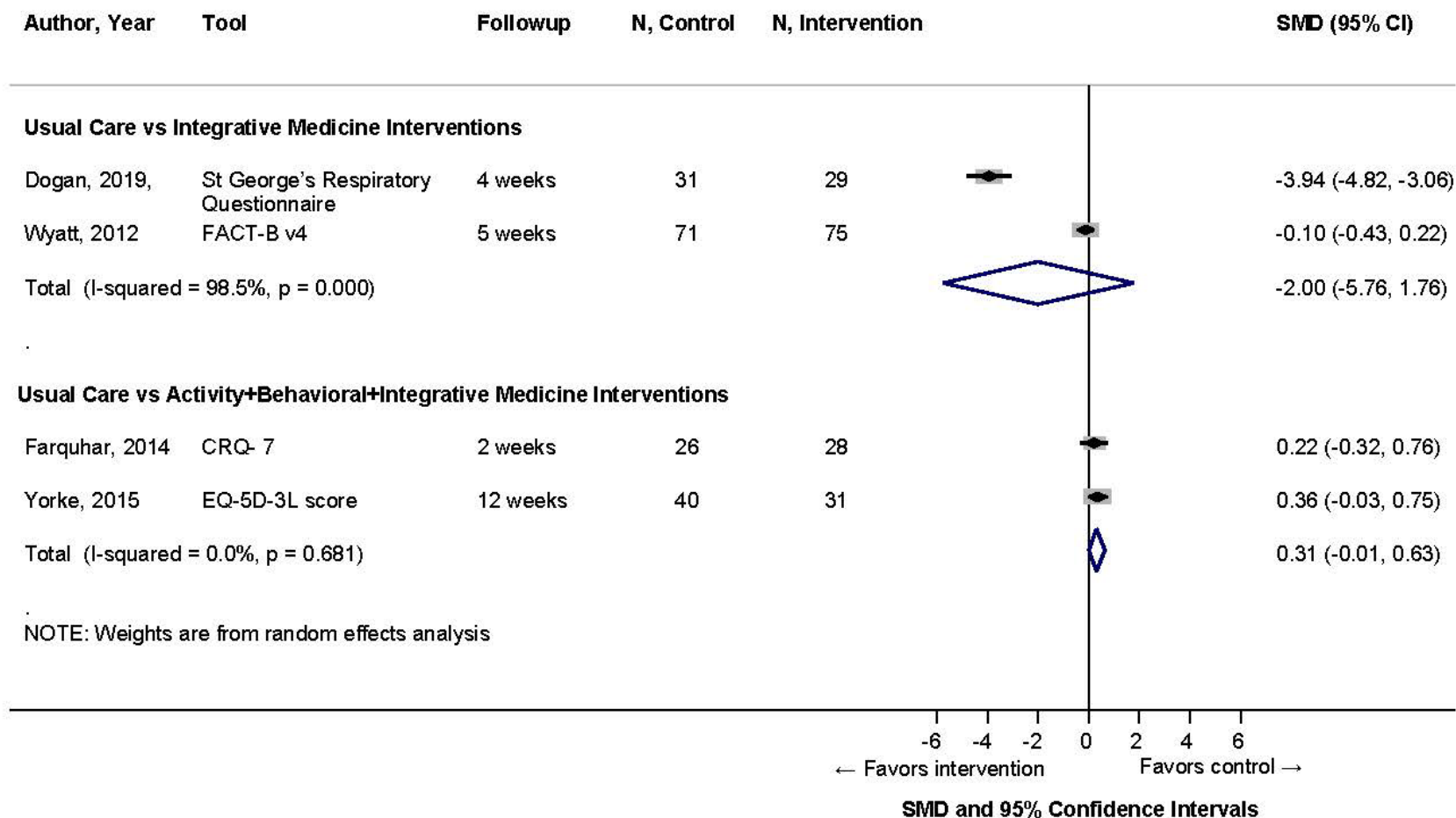


**SMD and 95% Confidence Intervals**

CI=confidence interval; HADS= Hospital Anxiety and Depression Scale; N=sample size; SMD=standardized mean difference



**Figure C-6. Meta-analysis of the effects of combined activity/rehabilitation, behavioral/psychoeducational, and integrative medicine interventions on quality of life in patients with advanced cancer in inpatient hospice or palliative care units**

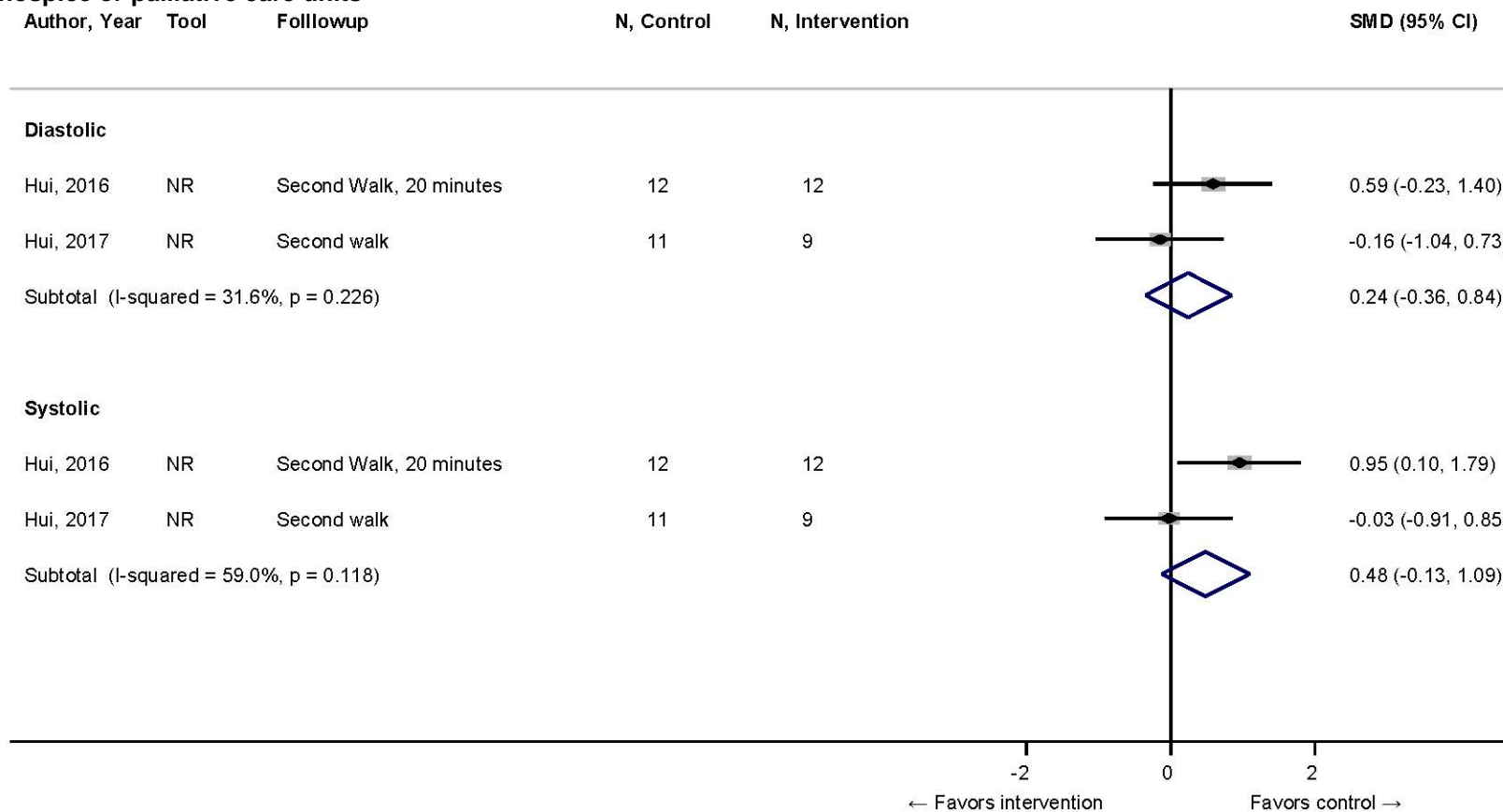


CI=confidence interval; CRQ=Chronic Respiratory Questionnaire; EQ-5D-3L=EuroQol-5D-3L test; FACT-B=Functional Assessment of Cancer Therapy-Breast; N=sample size; SMD=standardized mean difference



## Key Question 2: Meta-Analysis of Pharmacological Interventions

**Figure C-7. Meta-analysis of the effects of placebo versus opioids on blood pressure in patients with advanced cancer in inpatient hospice or palliative care units**

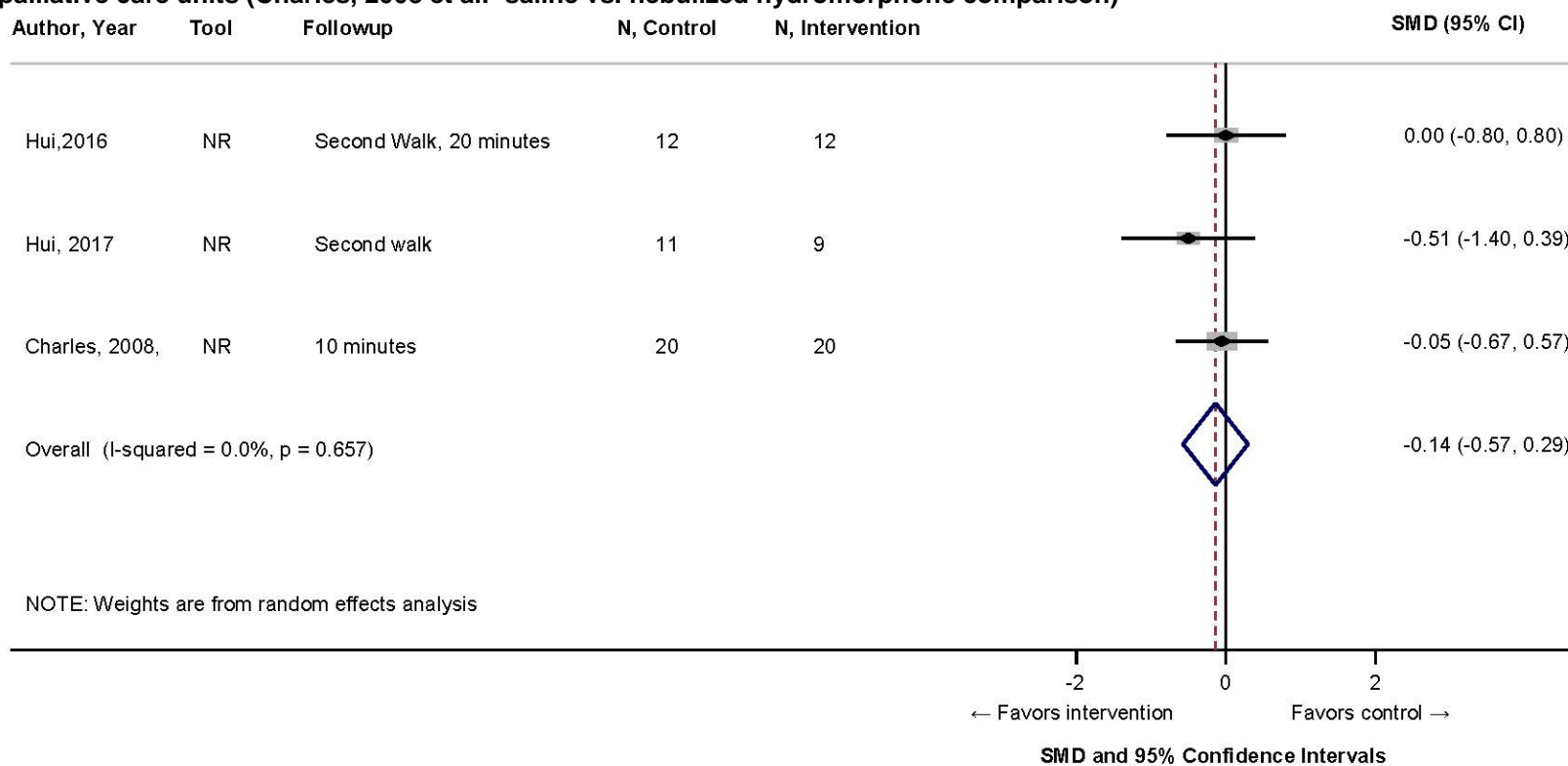


**SMD and 95% Confidence Intervals**

CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



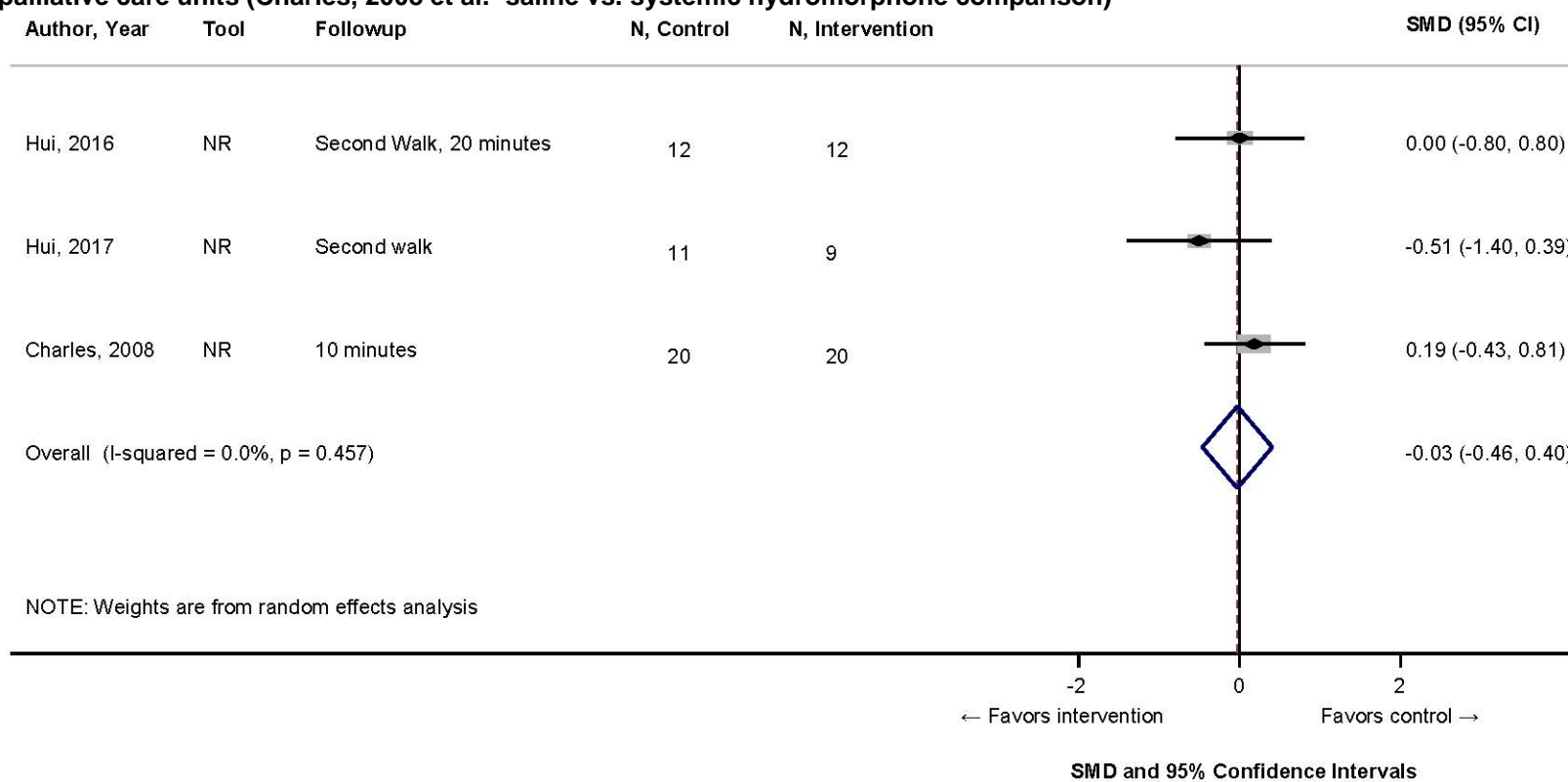
**Figure C-8. Meta-analysis of the effects of placebo versus opioids on heart rate in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.<sup>1</sup> saline vs. nebulized hydromorphone comparison)**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



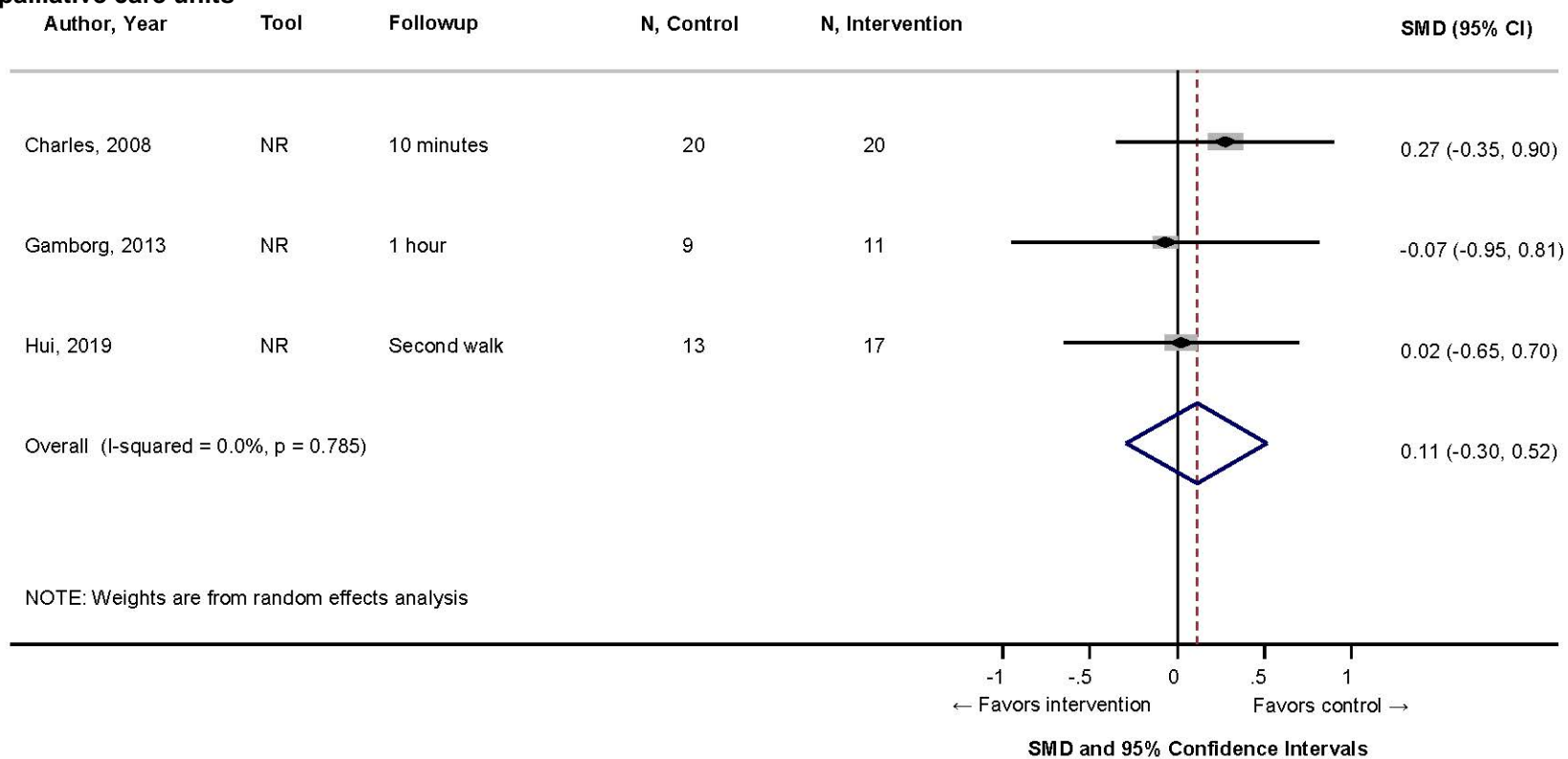
**Figure C-9. Meta-analysis of the effects of placebo versus opioids on heart rate in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.<sup>1</sup> saline vs. systemic hydromorphone comparison)**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



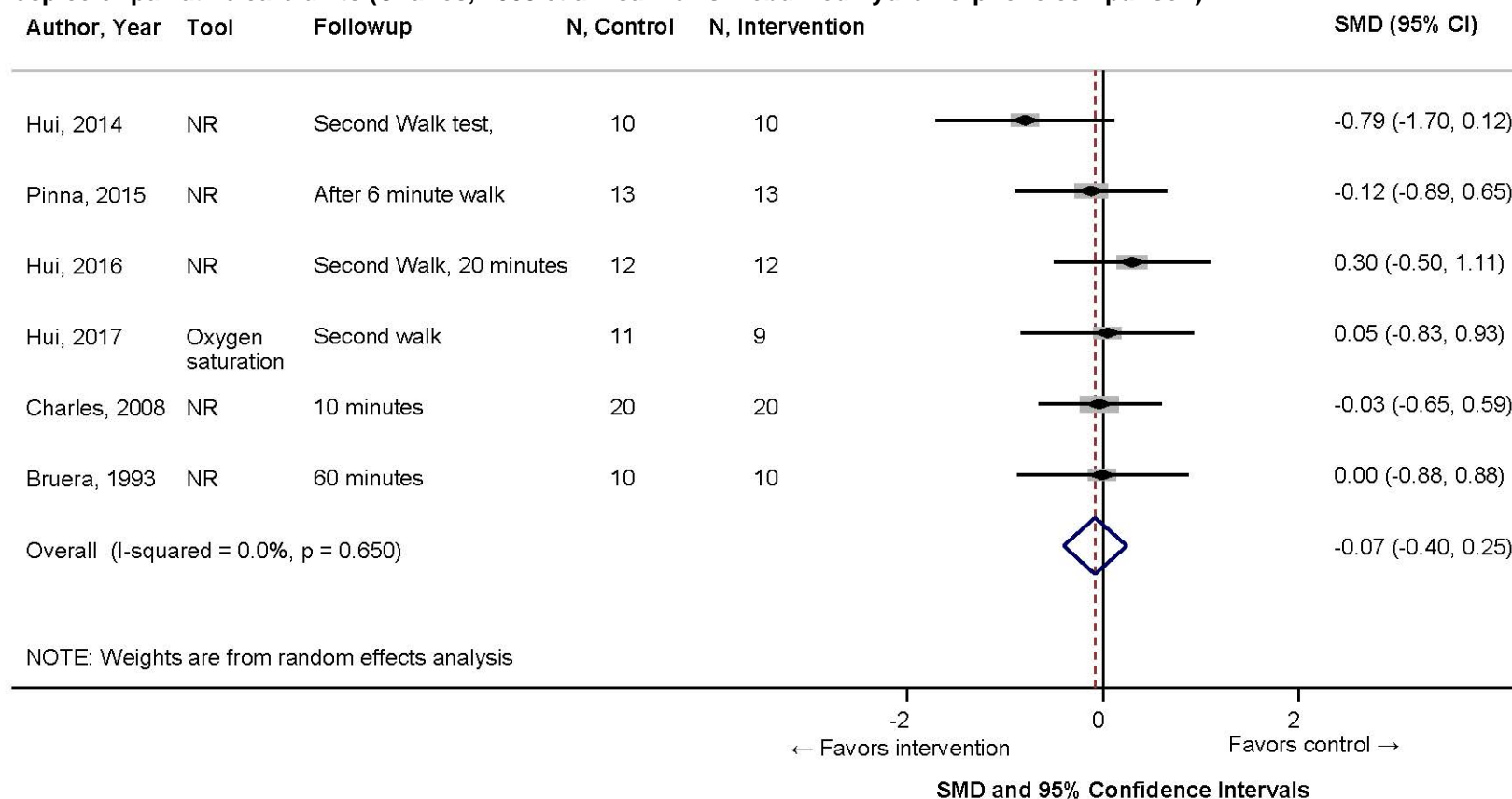
**Figure C-10. Meta-analysis of the effects of opioids versus opioids on heart rate in patients with advanced cancer in inpatient hospice or palliative care units**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



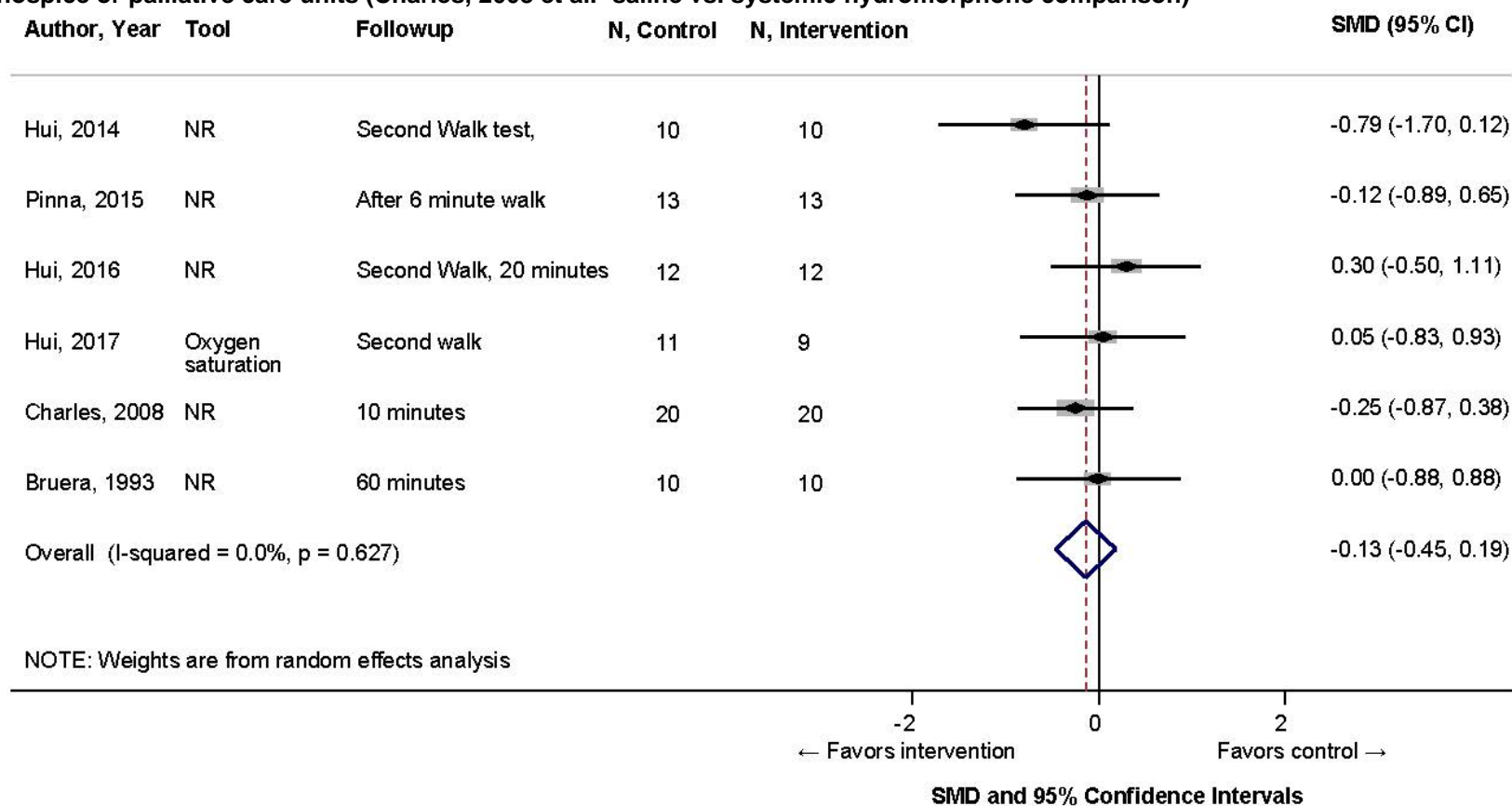
**Figure C-11. Meta-analysis of the effects of placebo versus opioids on oxygen saturation in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.<sup>1</sup> saline vs. nebulized hydromorphone comparison)**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



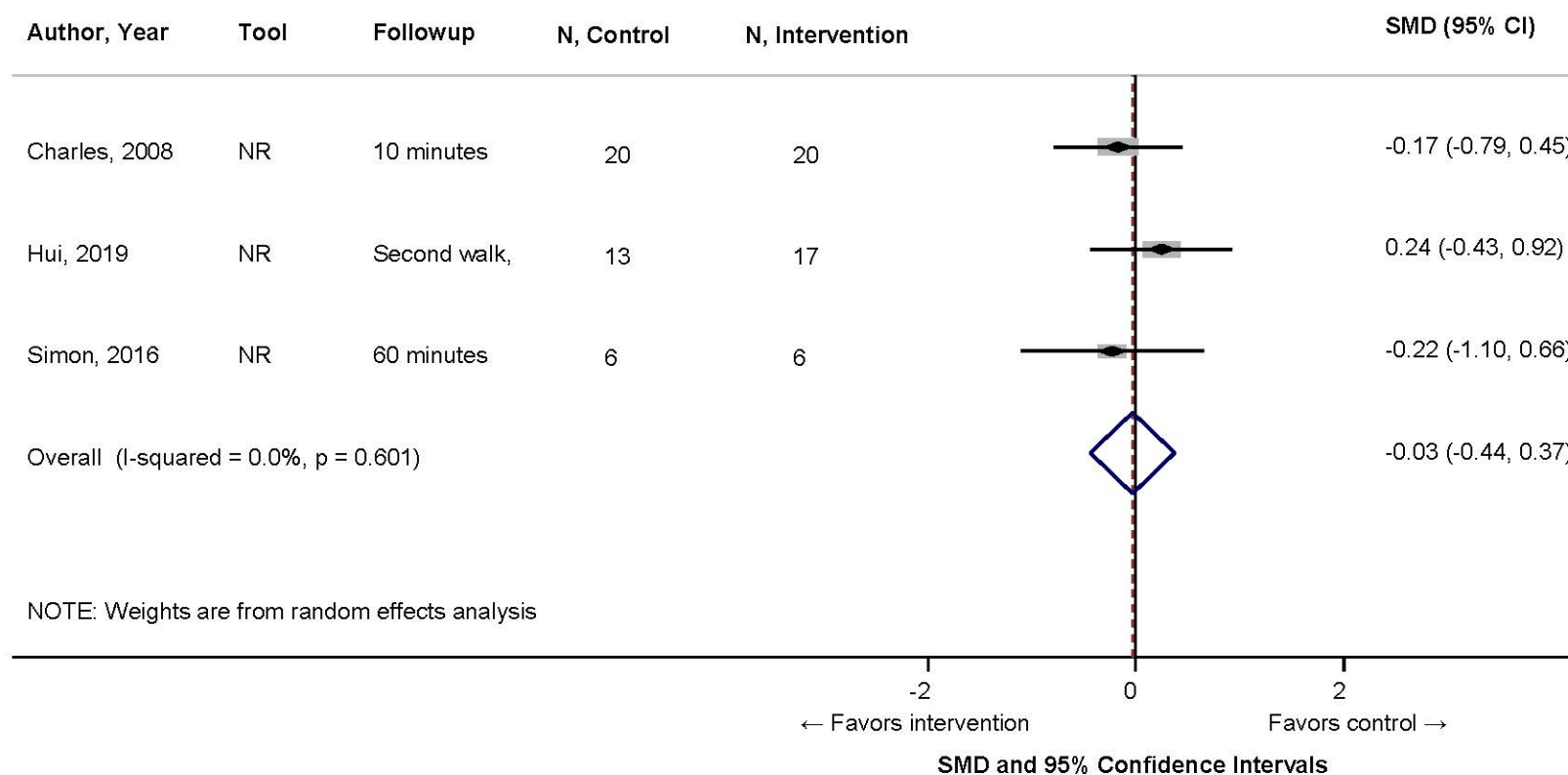
**Figure C-12. Meta-analysis of the effects of placebo versus opioids on oxygen saturation in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.<sup>1</sup> saline vs. systemic hydromorphone comparison)**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



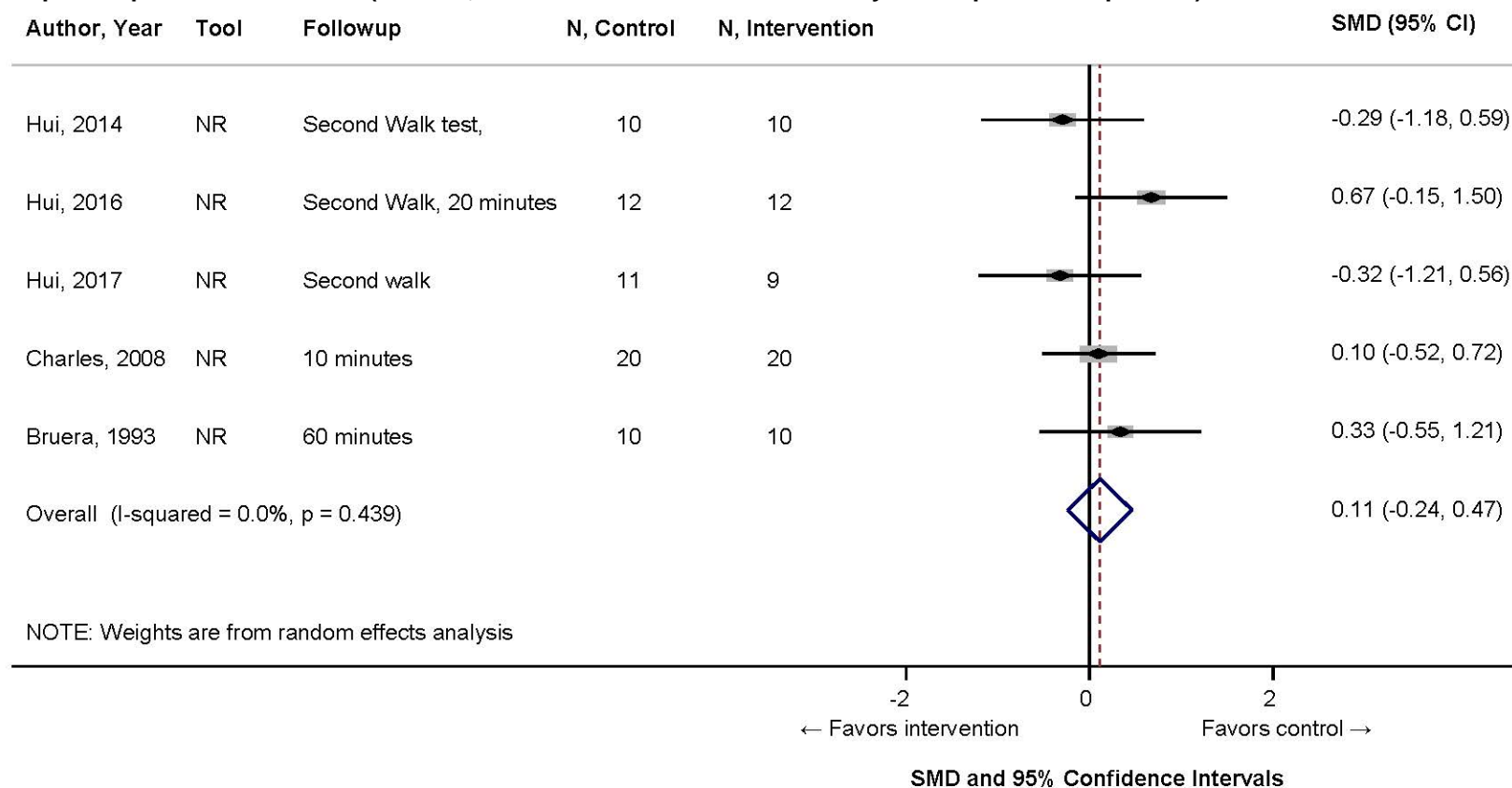
**Figure C-13. Meta-analysis of the effects of opioids versus opioids on oxygen saturation in patients with advanced cancer in inpatient hospice or palliative care units**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



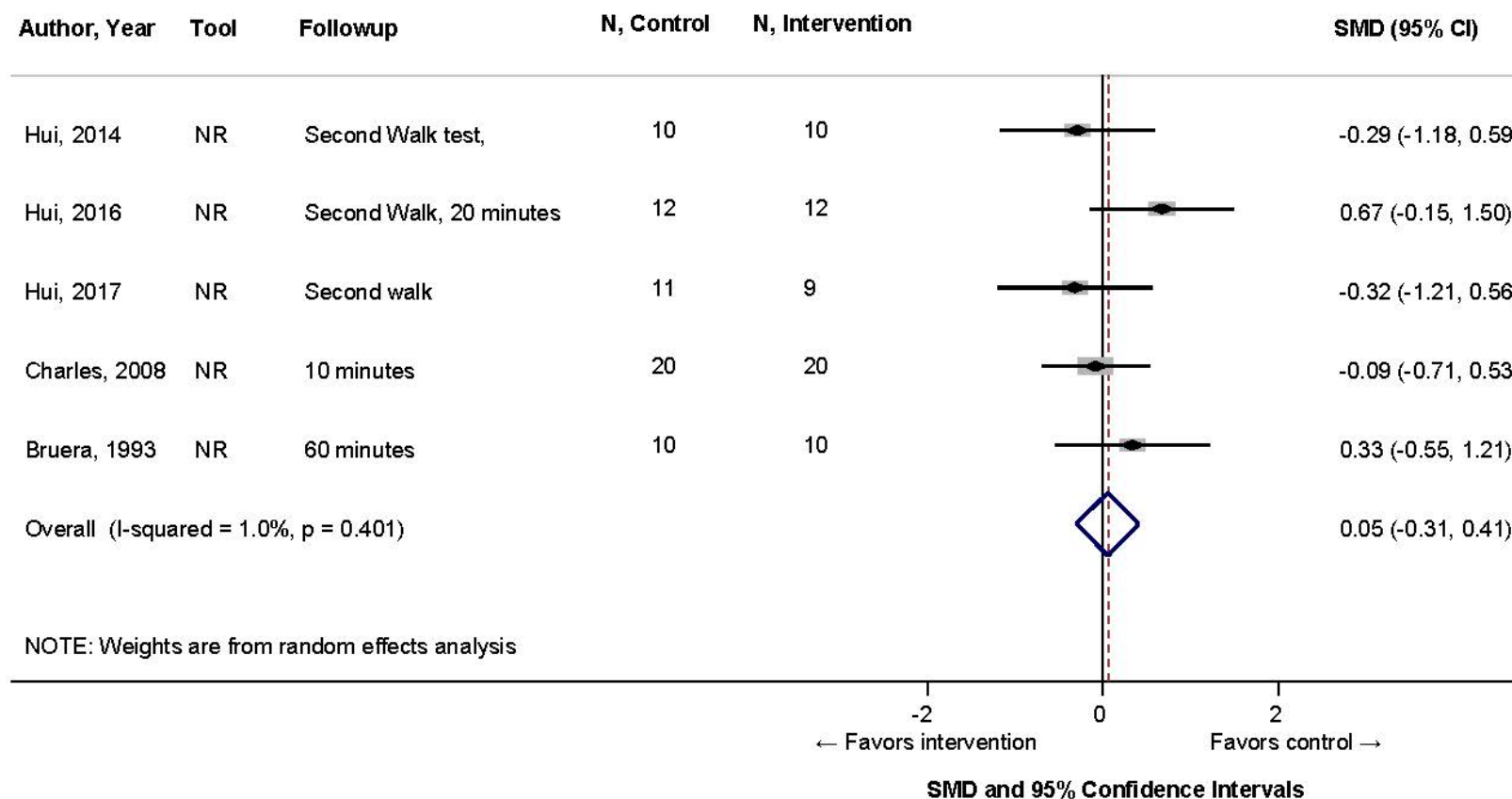
**Figure C-14. Meta-analysis of the effects of placebo versus opioids on respiratory rates in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.<sup>1</sup> saline vs. nebulized hydromorphone comparison)**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



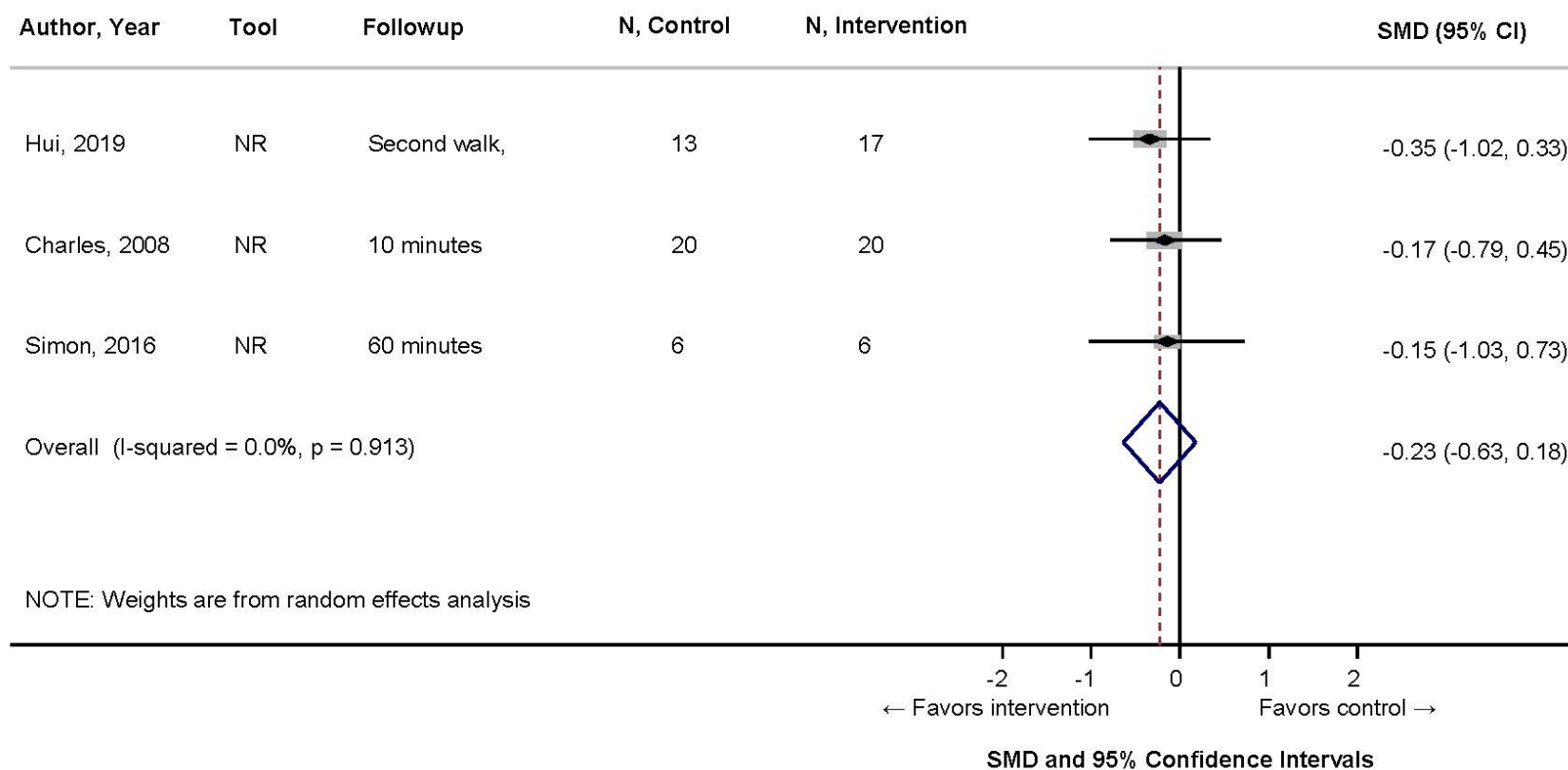
**Figure C-15. Meta-analysis of the effects of placebo versus opioids on respiratory rates in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.<sup>1</sup> saline vs. systemic hydromorphone comparison)**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



**Figure C-16. Meta-analysis of the effects of opioids versus opioids on respiratory rates in patients with advanced cancer in inpatient hospice or palliative care units**



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



### **Key Question 3: Meta-Analysis of Combination Non-Pharmacological and Pharmacological Interventions**

No meta-analysis calculated.



## **Key Question 4: Meta-Analysis of Harms Outcomes**

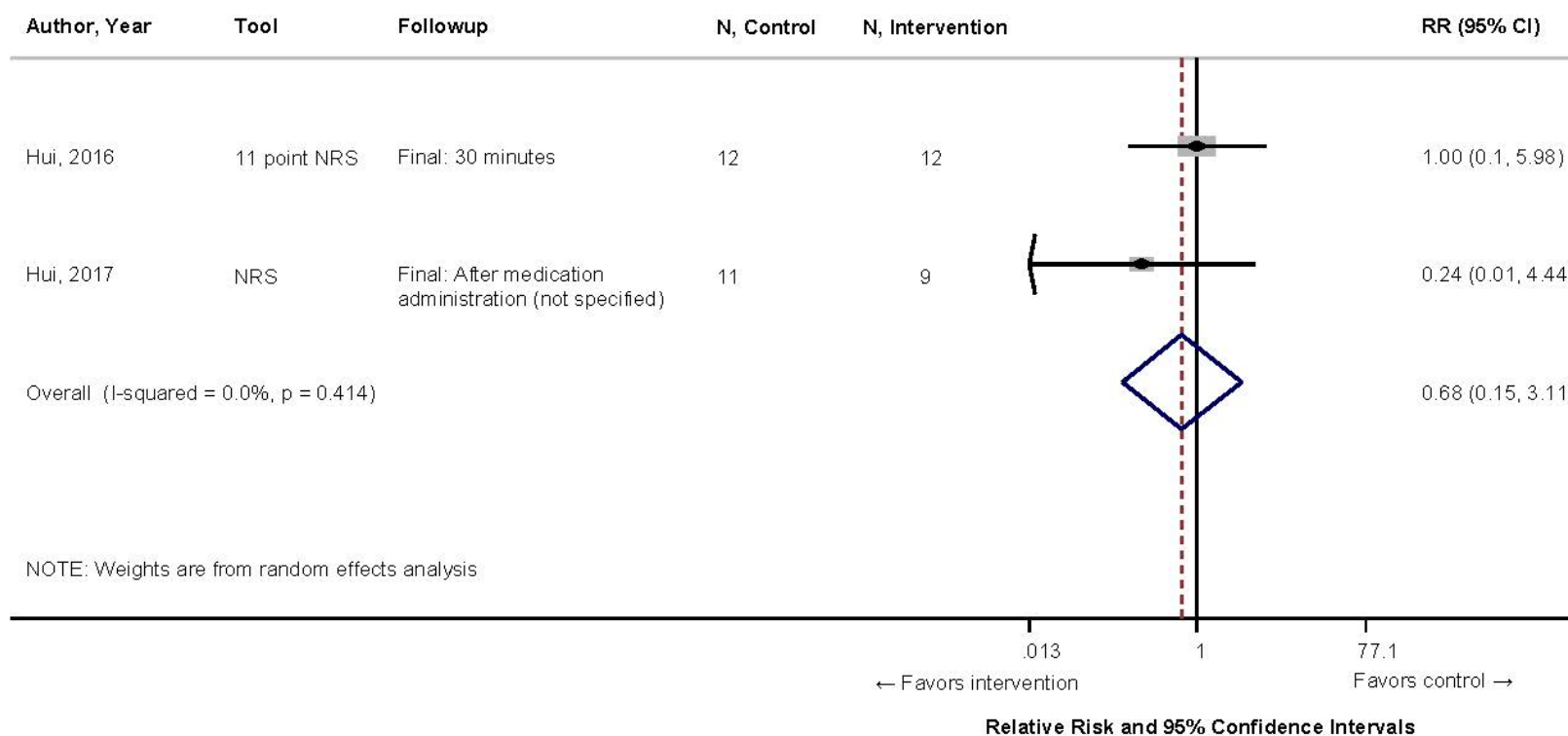
### **Meta-Analysis of Harms of Non-Pharmacological Interventions**

No meta-analysis calculated.



## Meta-Analysis of Harms of Pharmacological Interventions

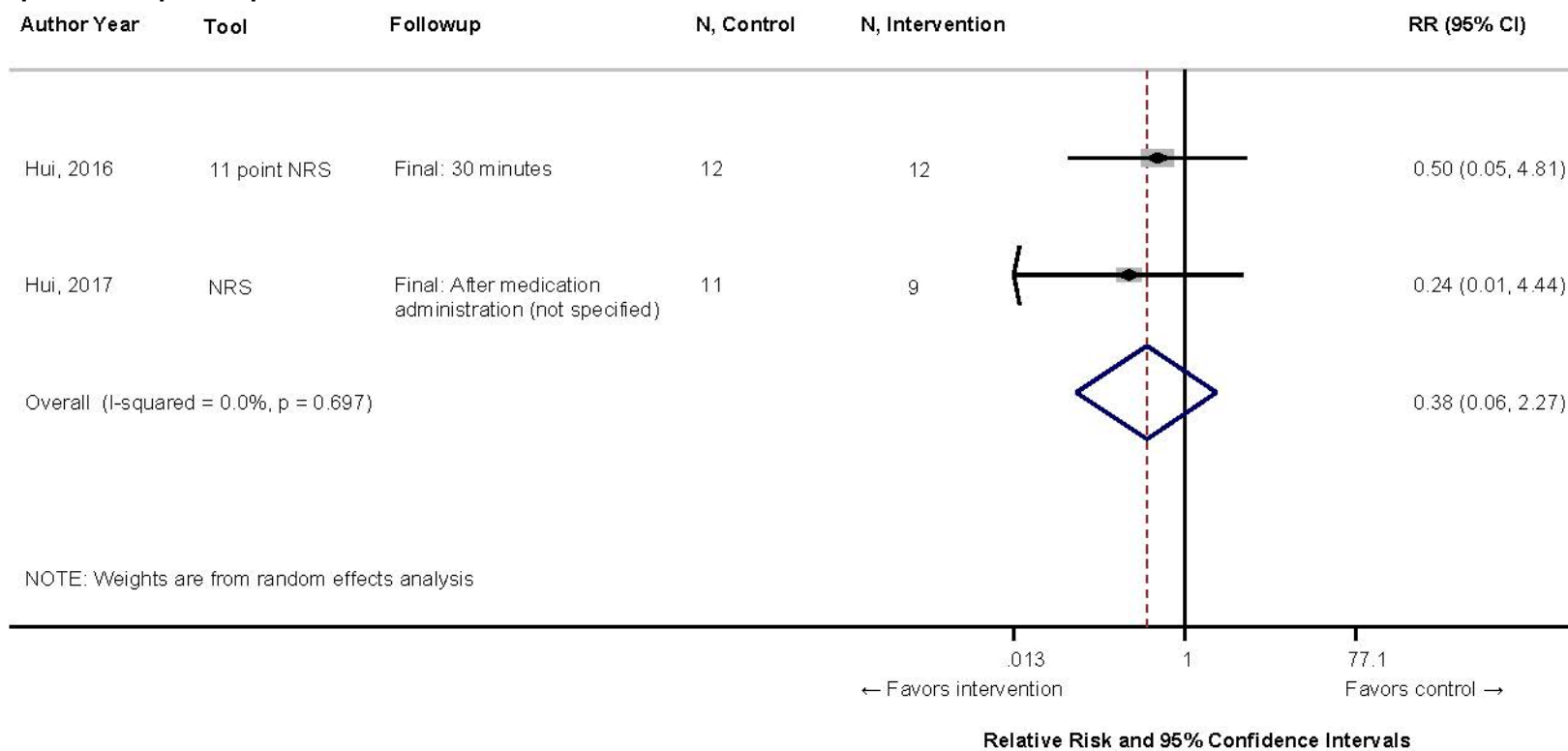
**Figure C-17. Meta-analysis of the effects of placebo versus opioids on dizziness outcomes in patients with advanced cancer in inpatient hospice or palliative care units**



CI=confidence interval; N=sample size; NR=not reported; NRS=Numerical Rating Scale; RR=relative risk



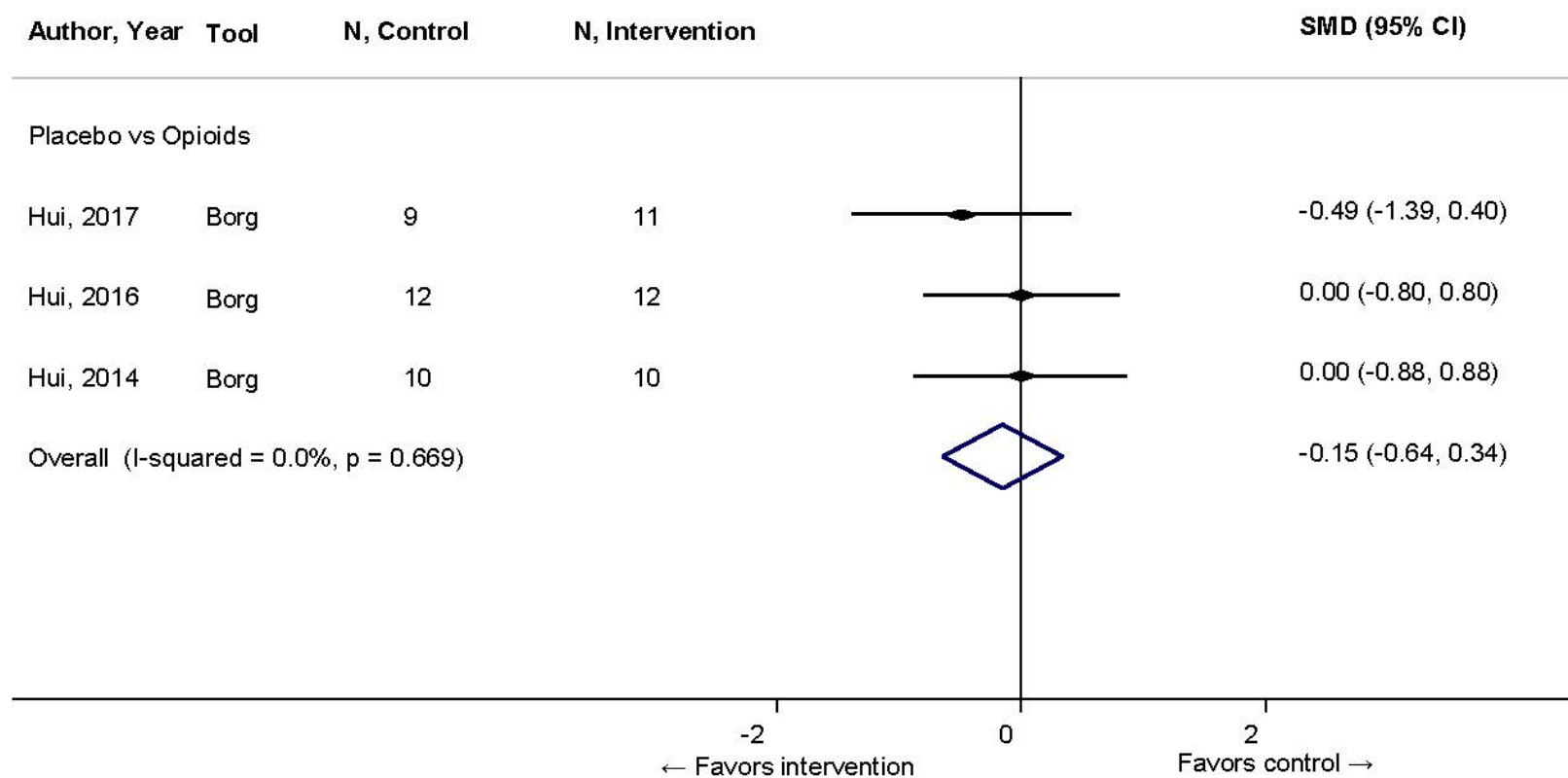
**Figure C-18. Meta-analysis of the effects of placebo versus opioids on drowsiness outcomes in patients with advanced cancer in inpatient hospice or palliative care units**



CI=confidence interval; N=sample size; NR=not reported; NRS=Numerical Rating Scale; RR=relative risk



**Figure C-19. Meta-analysis of the effects of placebo versus opioids on fatigue outcomes in patients with advanced cancer in inpatient hospice or palliative care units**



**SMD and 95% Confidence Intervals**

CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference



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# Appendix D. Evidence Tables

**Evidence Table D-1. Study design characteristics for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

<b>Author, Year</b>	<b>Included in KQ4</b>	<b>Followup</b>	<b>Study Design</b>	<b>Study Location</b>	<b>Study Setting</b>	<b>Single or Multicenter</b>	<b>Recruitment Start Year</b>	<b>Funding</b>
Booth, 1996 <sup>1</sup>	NR	15 minutes	RCT: Crossover	Europe	Hospice (inpatient)	Multi-center	NR	Non-profit
Bordeleau, 2003 <sup>2</sup>	KQ4	12 months	RCT	North America	Oncology clinic	Multi-center	1993	NR
Bruera, 1993 <sup>3</sup>	NR	5 minutes	RCT: Crossover	North America	NR	Single center	NR	NR
Bruera, 2003 <sup>4</sup>	KQ4	11 minutes	RCT: Crossover	North America	Oncology clinic	Single center	2001	NR
Chan, 2011 <sup>5</sup>	KQ4	12 weeks	RCT	Asia	Oncology clinic	Single center	NR	Government
Corner, 1996 <sup>6</sup>	KQ4	12 weeks	RCT	Europe	Oncology clinic	Single center	NR	Non-profit
Dhillon, 2017 <sup>7</sup>	KQ4	6 months	RCT	Australia	Hospital	Multi-center	2009	Government, Non-profit
Dogan, 2019 <sup>8</sup>	KQ4	4 weeks	RCT	Asia	Oncology clinic	Single center	2015	NR
Farquhar, 2014 <sup>9</sup>	KQ4	2 weeks	RCT: Crossover	Europe	Respiratory clinic	Single center	2008	Government, Non-profit
Henke, 2014 <sup>10</sup>	KQ4	9 weeks [exact NR, but says 3 cycles of chemotherapy, and cycles are 3 weekly]	RCT	Europe	Hospital (while getting chemo), continued at home	Single center	2010	NR
Hui, 2013 <sup>11</sup>	KQ4	2 hours	RCT	North America	Hospital	Single center	2007	Government
Hwang, 2012 <sup>12</sup>	NR	8 weeks	RCT	Asia	Oncology clinic	Single center	2010	NR



<b>Author, Year</b>	<b>Included in KQ4</b>	<b>Followup</b>	<b>Study Design</b>	<b>Study Location</b>	<b>Study Setting</b>	<b>Single or Multicenter</b>	<b>Recruitment Start Year</b>	<b>Funding</b>
Kako, 2018 <sup>13</sup>	NR	5 minutes	RCT	Asia	Inpatient palliative care unit	Single center	2016	Government
Ligibel, 2016 <sup>14</sup>	NR	16 weeks	RCT	North America	Oncology clinic	Multi-center	2006	Non-profit
McMillan, 2007 <sup>15</sup>	KQ4	30 days	RCT	North America	Hospice (home)	Single center	NR	Government
Molassiotis, 2015 <sup>16</sup>	KQ4	12 weeks	RCT	Europe	Oncology clinic	Multi-center	NR	Government
Moore, 2002 <sup>17</sup>	KQ4	3 months	RCT	Europe	Oncology clinic	Multi-center	NR	Government
Mosher, 2019 <sup>18</sup>	KQ4	6 weeks	RCT	North America	Oncology clinic	Single center	2016	Non-profit
Nakano, 2020 <sup>19</sup>	NR	6 days	RCT: Crossover	Asia	Hospital	Single center	2017	Government, Non-profit
Nava, 2013 <sup>20</sup>	KQ4	48 hours	RCT	Europe, Asia	ICU	Multi-center	2008	None
Philip, 2006 <sup>21</sup>	NR	15 minutes	RCT: Crossover	Australia	Oncology clinic, hospital	Multi-center	2001	Non-profit
Ramirez, 2018 <sup>22</sup>	NR	30 minutes	RCT	Europe	Inpatient palliative care unit	Single center	NR	Government, Non-profit
Rutkowska, 2019 <sup>23</sup>	NR	6 weeks	RCT	Europe	Hospital	Single center	2012	Not reported
Ting, 2020 <sup>24</sup>	NR	5 minutes	RCT: Crossover	Asia	Hospital, oncology clinic	Single center	2019	Not reported
Vanderbyl, 2017 <sup>25</sup>	KQ4	6 weeks	RCT: Crossover	North America	Oncology clinic	Single center	2009	Non-profit
Vickers, 2005 <sup>26</sup>	KQ4	1 week	RCT	North America	Hospital and oncology clinic	Single center	2001	Government
Wong, 2017 <sup>27</sup>	NR	5 minutes	RCT: Crossover	Asia	Hospice (inpatient)	Single center	2012	None
Wyatt, 2012 <sup>28</sup>	KQ4	11 weeks	RCT	North America	Oncology clinic	Multi-center	2006	Government
Yorke, 2015 <sup>29</sup>	KQ4	12 weeks	RCT	Europe	Clinic, Community (home, or hospital/ facility close to home)	Multi-center	2013	Non-profit

ICU=intensive care unit; KQ4=Key Question 4; NR=not reported; RCT=randomized clinical trial



**Evidence Table D-2. Study design characteristics for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Followup	Study Design	Study Location	Study Setting	Single Or Multicenter	Recruitment Start Year	Funding
Aabom, 2019 <sup>30</sup>	NR	20 minutes	RCT: Crossover	Europe	Palliative care clinic	Multi-center	2016	Non-profit
Allard, 1999 <sup>31</sup>	NR	240 minutes	RCT	North America	Palliative care clinic	Multi-center	1994	Government
Bruera, 1993 <sup>32</sup>	NR	60 minutes	RCT: Crossover	North America	Not reported	Single center	NR	Not reported
Bruera, 2005 <sup>33</sup>	KQ4	2 days	RCT: Crossover	North America, South America, Australia	NR	Multi-center	NR	NR
Charles, 2008 <sup>34</sup>	KQ4	60 minutes	RCT: Crossover	Australia	Hospice (home), Hospice (inpatient)	Single center	NR	Non-profit
Gamborg, 2013 <sup>35</sup>	KQ4	1 hour	RCT	Europe	Hospice (inpatient)	Single center	2006	Non-profit
Hardy, 2016 <sup>36</sup>	KQ4	14 days	RCT	Australia, New Zealand	Hospital, Hospice (inpatient)	Multi-center	2009	Non-profit
Hui, 2014 <sup>37</sup>	KQ4	160 minutes	RCT	North America	Oncology clinic	Single center	2012	Non-profit
Hui, 2016 <sup>38</sup>	KQ4	172 minutes	RCT	North America	Palliative care clinic	Single center	2013	Government, Non-profit, Industry
Hui, 2016 <sup>39</sup>	KQ4	14 days	RCT	North America	Oncology, Palliative care clinic	Single center	2013	Government, Non-profit
Hui, 2017 <sup>40</sup>	KQ4	6 minutes	RCT	North America	Palliative care clinic	Single center	2014	Government, Non-profit, Industry
Hui, 2019 <sup>41</sup>	KQ4	NR	RCT	North America	Oncology, Palliative care clinic	Single center	2016	Industry, Government, Non-profit
Kawabata, 2013 <sup>42</sup>	KQ4	NR	Retrospective cohort	Asia	Palliative care clinic	Single center	2008	No financial support for the research, authorship, and/or publication of this article
Navigante, 2006 <sup>43</sup>	KQ4	48 hours	RCT	South America	Hospital	Single center	NR	Non-profit
Navigante, 2010 <sup>44</sup>	KQ4	5 Days	RCT	South America	Oncology clinic	Single center	NR	Non-profit
Peoples, 2016 <sup>45</sup>	NR	28 days	RCT	North America	Oncology clinic	Multi-center	2002	Government
Pinna, 2015 <sup>46</sup>	KQ4	7 Days	RCT: Crossover	Europe	Palliative care clinic	Single center	2011	No funding
Simon, 2016 <sup>47</sup>		60 minutes	RCT: Crossover	Europe	Inpatient	Multi-center	2013	Government, industry
Tian, 2016 <sup>48</sup>	KQ4	60 minutes	Retrospective cohort	Asia	Hospital	Single center	2011	Government

ICU=intensive care unit; KQ4=Key Question 4; NR=not reported; RCT=randomized clinical trial



**Evidence Table D-3. Study design characteristics for studies comparing combination of non-pharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Followup	Study Design	Study Location	Study Setting	Single Or Multicenter	Recruitment Start Year	Funding
Gottlieb, 2020 <sup>49</sup>	NR	14 days	RCT	Europe	Unspecified outpatient clinics	Single center	2006	Government, Nonprofit
Minchom, 2016 <sup>50</sup>	KQ4	14 days	RCT	Europe	Unspecified outpatient clinics	Single center	2006	Government, Nonprofit

KQ4=Key Question 4; RCT=randomized clinical trial



**Evidence Table D-4. Inclusion criteria for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Followup	Study Design	Baseline Breathlessness Score Inclusion Criteria	Functional Status Inclusion Criteria	Life Expectancy Inclusion Criteria	Other Inclusion Criteria
Booth, 1996 <sup>1</sup>	NR	15 minutes	RCT: Crossover	NR	NR	NR	Inpatients with advanced cancer, no prior oxygen needs.
Bordeleau, 2003 <sup>2</sup>	KQ4	12 months	RCT	NR	NR	> 3 months	Women with metastatic breast cancer (but not CNS metastasis), no active psychiatric comorbidities, English speaking, no other ongoing trial participation, living within 1 hour of study center.
Bruera, 1993 <sup>3</sup>	NR	5 minutes	RCT: Crossover	NR	NR	"terminal"	Advanced cancer, terminal, hypoxemia (<90% O2 sat if on room air for 5 minutes), oxygen needs <4L/ minute.
Bruera, 2003 <sup>4</sup>	KQ4	11 minutes	RCT: Crossover	≥3/10 on NRS	'Ambulatory'	NR	Advanced cancer, ambulatory, normal condition, hemoglobin ≥ 10g/dL, COPD ok if no oxygen, no acute respiratory distress, no oxygen need over last 4 weeks, O2 sat >90%, no obvious cause of dyspnea such as heart failure or pericardial effusion.
Chan, 2011 <sup>5</sup>	KQ4	12 weeks	RCT	NR	KPS>60%	NR	Age ≥ 16, stage 3/4 lung cancer with plan for palliative RT, Chinese speaking, normal condition, no psychiatric comorbidity and not on other clinical trial.
Corner, 1996 <sup>6</sup>	KQ4	12 weeks	RCT	NR	NR	NR	Advanced lung cancer with dyspnea attending clinic after completing chemotherapy/ radiotherapy.
Dhillon, 2017 <sup>7</sup>	KQ4	6 months	RCT	NR	ECOG ≤2	>6 months	Advanced lung cancer, ECOG PS0-2, English speaking, medically fit by treating physician and Physical Activity Readiness Questionnaire (PAR-Q)
Dogan, 2019 <sup>8</sup>	KQ4	4 weeks	RCT	≥3/10 on modified borg scale	NR	> 3 months	Age ≥18, newly diagnosed lung cancer, literate, no other lung disease (asthma/ COPD), hemoglobin >8 g/dL, no cardiac dysfunction, no contraindication to acupressure such as pancytopenia or nerve/ tissue/ vascular disease in areas of acupressure
Farquhar, 2014 <sup>9</sup>	KQ4	2 weeks	RCT: Crossover	NR	NR	NR	Advanced cancer referred to breathless service.
Henke, 2014 <sup>10</sup>	KQ4	9 weeks [	RCT	NR	KPS>50%	NR	Age ≥18, stage 3 or 4 lung cancer, receiving inpatient chemo, not on similar trial, no epilepsy or severe cardiovascular disease, no rheumatic disorder, not confined to bed.
Hui, 2013 <sup>11</sup>	KQ4	2 hours	RCT	≥3/10 (average dyspnea at rest over the past week, on NRS) despite standard supplemental oxygen	NR	>1 week	Hospitalized, age ≥18, advanced cancer (locally advanced or metastatic), English speaking, no hemodynamic instability, no acute respiratory distress with impending intubation, no delirium (Memorial Delirium Assessment Scale >13/30), Glasgow coma scale should be ≥8/15, no contraindication to bipap, no non-cancer related dyspnea needing home oxygen prior to hospitalization.



Author, Year	Included in KQ4	Followup	Study Design	Baseline Breathlessness Score Inclusion Criteria	Functional Status Inclusion Criteria	Life Expectancy Inclusion Criteria	Other Inclusion Criteria
Hwang, 2012 <sup>12</sup>	NR	8 weeks	RCT	NR	ECOG 0-1	NR	Age 40-75, advanced stage primary lung adenocarcinoma with EGFR mutations for >4 weeks, no diabetes, no clinical instability, no severe cardiac/ musculoskeletal condition, able to understand instructions.
Kako, 2018 <sup>13</sup>	NR	5 minutes	RCT	≥3 on NRS	ECOG 3 or 4	NR	No current/ planned cancer treatment, age ≥ 20, peripheral oxygen saturation levels of>90%, cognitive intact and able to communicate in Japanese, hemoglobin >6g/dL, no fever in last 24 hours, no disease of trigeminal nerve.
Ligibel, 2016 <sup>14</sup>	NR	16 weeks	RCT	NR	ECOG 0-1	>12 months	Advanced breast cancer not amenable to surgical resection, baseline <150 min of recreational activity per week, no untreated brain metastases or cardiac disease or other contraindications to moderate-intensity exercise. Patients with bony metastatic disease were allowed to participate in the study.
McMillan, 2007 <sup>15</sup>	KQ4	30 days	RCT	NR	Palliative Performance Scale >40%	NR	Hospice patients with cancer, identified caregiver, at least 2 of pain, dyspnea, constipation, 6th grade education, speak English.
Molassiotis, 2015 <sup>16</sup>	KQ4	12 weeks	RCT	NR	NR	> 3 months	Primary lung cancer or mesothelioma, refractory dyspnea at rest or minimal exertion for 3 months, O2 sat >85% at rest, no unstable COPD or unstable angina or acute dyspnea needing intervention, no chemo or radiation in last 2-4 weeks and no concurrent treatment with chemo/ RT, no intractable cough or pleural effusion needing drainage.
Moore, 2002 <sup>17</sup>	KQ4	3 months	RCT	NR	Not "poor PS"	> 3 months	No active anticancer therapy, not requiring close medical supervision.
Mosher, 2019 <sup>18</sup>	KQ4	6 weeks	RCT	Rotterdam Symptom item score ≥ 2 for anyone of dyspnea (or fatigue, pain, sleep etc.)	ECOG 0-2	NR	Age ≥18, advanced lung cancer, caregiver who reported at least subclinical distress, no severe cognitive impairment, not on hospice, English speaking.
Nakano, 2020 <sup>19</sup>	NR	6 days	RCT: Crossover	NR	NR	NR	Advanced cancer, cancer-related pain (not orthopedic or dental pain), receiving palliative care, informed consent, >20 years age, no pacemaker and no ischemic heart disease, no electrical hypersensitivity or epilepsy, no skin lesions at treatment sites, able to communicate.



Author, Year	Included in KQ4	Followup	Study Design	Baseline Breathlessness Score Inclusion Criteria	Functional Status Inclusion Criteria	Life Expectancy Inclusion Criteria	Other Inclusion Criteria
Nava, 2013 <sup>20</sup>	KQ4	48 hours	RCT	≥4/10 on borg scale	NR	<6 months	End-stage solid cancer, partial pressure oxygen/ fraction of inspired oxygen< 1:250, signs of respiratory distress or respiratory rate >30/minute or ≥4/10 on borg scale, competent (Kelly score<4), no other reversible cause (COPD/ CHF), no treatment refusal. no weak cough reflex, no agitation, no cardiac ischemia/ arrhythmia, no organ failure of 2 or more organs, no opioids within 2 weeks, no history of addiction/ intolerance of opioids, no acute kidney injury or head trauma.
Philip, 2006 <sup>21</sup>	NR	15 minutes	RCT: Crossover	≥30/100 on VAS	NR	NR	Inpatient and outpatients with advanced cancer, stable medication (including opioids), normal mental status, age >18, no contraindication to oxygen and not oxygen dependent, no acute respiratory distress.
Ramirez, 2018 <sup>22</sup>	NR	30 minutes	RCT	NR	NR	"terminal"	Advanced cancer, admitted to palliative care unit, understanding Spanish/ Catalan language, no deafness or cognitive impairment, no agony/ unresponsiveness/ restlessness/ agitation
Rutkowska, 2019 <sup>23</sup>	NR	6 weeks	RCT	NR	WHO PS 0-1	NR	Advanced lung cancer diagnosed <6 weeks ago, able to perform 6MWT, able to exercise, no uncontrolled hypertension or heart disease, he,oglobin >10g/ DL, no severe arthritis, and no bone/ CNS metastases
Ting, 2020 <sup>24</sup>	NR	5 minutes	RCT: Crossover	Modified Borg Scale ≥ 3	ECOG 3 or 4	NR	Advanced (metastatic or locally advanced), ≥18 years old, no cognitive impairment, no fever, Hb>8g/dL, no disease of trigeminal nerve, intubated patients were included as long as their RR was higher than the set ventilation backup rate if they were on assist-control mode, and they were able to give their MBS score.
Vanderbyl, 2017 <sup>25</sup>	KQ4	6 weeks	RCT: Crossover	NR	ECOG 0-2	>4 months	>18 years, advanced GI or lung cancer, able to exercise, no active psychiatric condition, no severe heart, skeletal, neuromuscular condition, no brain mets.
Vickers, 2005 <sup>26</sup>	KQ4	1 week	RCT	American Thoracic Society Breathlessness score 2 or higher	NR	'if likely to survive course of trial'	Age ≥18, advanced breast or lung cancer, should have trialed steroids if indicated, no history of asthma, symptoms should be >7 days, hemoglobin >8 g/dL, no recent acupuncture, no contraindication to acupuncture like pancytopenia/ heart valve dysfunction, on stable cancer therapy with no planned initiation/ changes, no other clear cause of dyspnea like CHF/ sarcoid/ pneumothorax.
Wong, 2017 <sup>27</sup>	NR	5 minutes	RCT: Crossover	≥3/10 on NRS	NR	NR	Advanced cancer, inpatient palliative care unit, mentally competent and able to express dyspnea, no fever/ acute difficulty in breathing, and willing to participate.



<b>Author, Year</b>	<b>Included in KQ4</b>	<b>Followup</b>	<b>Study Design</b>	<b>Baseline Breathlessness Score Inclusion Criteria</b>	<b>Functional Status Inclusion Criteria</b>	<b>Life Expectancy Inclusion Criteria</b>	<b>Other Inclusion Criteria</b>
Wyatt, 2012 <sup>28</sup>	KQ4	11 weeks	RCT	NR	Able to perform basic ADLs'	Score of 11 or lower on the Palliative prognostic score, which indicates a 30% probability of having a life expectancy >3 months	Age ≥21, stage 3 or 4 breast cancer, cognitive impact, speak English, have telephone, receiving chemo or some hormonal treatment, not in hospice/ nursing home/ care facility, not bedridden, not on other clinical trial, not using other CAM measures as in protocol.
Yorke, 2015 <sup>29</sup>	KQ4	12 weeks	RCT	NR	WHO PS 0-2	>3 months	Primary lung cancer, "bothered" by dyspnea/cough/fatigue, no recent COPD exacerbation or pneumonia, no anticancer treatment in past 4-6 weeks.

CAM= Confusion Assessment Method; CHF=chronic heart failure; CNS=central nervous system; COPD= Chronic obstructive pulmonary disease; ECOG= Eastern Cooperative Oncology Group Performance Status; EGFR=estimated glomerular filtration rate; GI=gastrointestinal; ICU=intensive care unit; KQ4=Key Question 4; KPS= Karnofsky Performance Score; KQ4=Key Question 4; NR=not reported; NRS=numerical rating scale; O2=oxygen; RCT=randomized clinical trial; RR=respiratory rate; RT=radiotherapy; VAS=visual analog scale; WHO=World Health Organization



**Evidence Table D-5. Inclusion criteria for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Followup	Study Design	Baseline Breathlessness Score Inclusion Criteria	Functional Status Inclusion Criteria	Life Expectancy Inclusion Criteria	Other Inclusion Criteria
Aabom, 2019 <sup>30</sup>	NR	20 minutes	RCT: Crossover	NR	(EORTC) QLQ-C15-PAL score 1, or ESAS score 3 and ECOG status 0-2, Karnofsky performance status >50%	≥1 month	Diagnosis of cancer; outpatients at the Palliative Care, Zealand University Hospital or Hospice Zealand; aged 18 or older, ambulatory (with or without walking aid), either opioid naive or with a stable dose of strong opioids and no rescue medicine in the week of trial, no cortisone, and non-anemic (hemoglobin > 6), no patients with intolerance or allergy to opioids, no contradiction to completing the 2-min walk test, no glomerular filtration rates less than 50 (ml/min/173 m2), no severe hepatic impairment, and no pregnant women or nursing mothers
Allard, 1999 <sup>31</sup>	NR	240 minutes	RCT	Dyspnea intensity at 90 minutes measured at least 2.0 (VAS)	No cognitive impairment according to a simplified Folstein Mini-Mental State Examination	NR	Had persistent dyspnea at rest, they were already regularly receiving opioids for pain relief, they were alert and not confused, there was no contraindication to study participation, they were not in acute respiratory distress for which an immediate intervention was mandatory, had not received three or more rescue doses for breakthrough pain during the previous 24 hours, they were not receiving only so-called “weak” opioids (codeine and codeine derivatives) or fentanyl for pain relief.
Bruera, 1993 <sup>32</sup>	NR	60 minutes	RCT: Crossover	NR	NR	NR	Terminal cancer patients
Bruera, 2005 <sup>33</sup>	KQ4	2 days	RCT: Crossover	Resting baseline dyspnea ≥3 on 0-10 scale (not specified)	NR	NR	Dyspnea related to advanced cancer with a predominant restrictive ventilation, receiving regular oral or parenteral opioids w/p change for 72 hours, normal cognition status, no contraindication to morphine, dyspnea not related to an acute complication.
Charles, 2008 <sup>34</sup>	KQ4	60 minutes	RCT: Crossover	NR	NR	≥7 days	Needed to be able to provide informed consent in English, ≥18 years of age, to have a primary diagnosis of cancer with a clinical prognosis of at least seven days, MMSE score of at least 24 out of 30, incident dyspnea with no reversible components on a background of either irreversible dyspnea at rest or development of dyspnea when they spoke, and to be using a stable regular dose of an opioid.



Author, Year	Included in KQ4	Followup	Study Design	Baseline Breathlessness Score Inclusion Criteria	Functional Status Inclusion Criteria	Life Expectancy Inclusion Criteria	Other Inclusion Criteria
Gamborg, 2013 <sup>35</sup>	KQ4	1 hour	RCT	Resting dyspnea $\geq 3$ VAS	NR	NR	Has dyspnea related to advanced primary or metastatic lung cancer, on regular oral or parenteral opioids for pain, ability to understand the purpose and content of the study, no causal treatment of the cancer or the dyspnea possible, no treatment with methadone, ability to take oral medicine, no administration of oxygen with change within 20 minutes before study start, no administration of short-acting opioids within 4 hours of study start, no administration of inhaled medicine within 20 minutes before study start.
Hardy, 2016 <sup>36</sup>	KQ4	14 days	RCT	Dyspnoea score of $\geq 3/10$ (scale not specified)	AKPS $>30$	NR	Dyspnoea related to life-limiting disease, able to operate a nasal spray device, complete a dyspnoea diary, understand trial requirements, no changes in any medication likely to affect dyspnoea within 48 h of study entry, no acute respiratory event (e.g. chest infection, acute exacerbation of asthma), no concurrent treatment with an unstable dose of benzodiazepines (excluding nocturnal sedation), no concurrent treatment with an unstable dose of opioids, no regular use ( $>3$ times/day) of breakthrough opioids, no previous adverse reaction to benzodiazepines, no intervention/change in therapy likely to effect dyspnoea during the study period or in the 2 weeks prior.
Hui, 2014 <sup>37</sup>	KQ4	160 minutes	RCT	Average intensity of breakthrough dyspnea $\geq 3/10$ (NRS), Patients with dyspnea at rest $\leq 7/10$	NR	NR	Outpatient at the Supportive Care Center at M. D. Anderson Cancer Center, age 18 or older, ability to communicate in English or Spanish, ambulatory with or without walking aid, Karnofsky Performance Status score $\geq 50\%$ , and a stable dose of strong opioids with a morphine equivalent daily dose (MEDD) of between 30 mg and 580 mg, no standard supplemental oxygen $>6$ L/minute, delirium (Memorial Delirium Assessment Scale $>13/30$ ), allergic reaction to fentanyl, no history of substance abuse, no recent history of coronary artery disease, no uncontrolled tachycardia or hypertension at the time of assessment.
Hui, 2016 <sup>38</sup>	KQ4	172 minutes	RCT	Average intensity of episodic dyspnea $3/10$ on NRS) no patients with dyspnea NRS at rest $\geq 7/10$	Karnofsky performance status $\geq 50\%$	NR	Diagnosis of cancer, outpatients at the Supportive Care Center at MD Anderson Cancer Center, age 18 or older, ambulatory with or without walking aid, and a stable dose of strong opioids with an morphine equivalent daily dose (MEDD) of between 80 mg/day and 500 mg/day. No patients with standard supplemental oxygen $>6$ L/minute, delirium (i.e. Memorial Delirium Assessment Scale $>13/30$ ), allergic reaction to fentanyl, history of opioid abuse, or contraindications to completing the 6 minute walk test (6MWT).



<b>Author, Year</b>	<b>Included in KQ4</b>	<b>Followup</b>	<b>Study Design</b>	<b>Baseline Breathlessness Score Inclusion Criteria</b>	<b>Functional Status Inclusion Criteria</b>	<b>Life Expectancy Inclusion Criteria</b>	<b>Other Inclusion Criteria</b>
Hui, 2016 <sup>39</sup>	KQ4	14 days	RCT	Average dyspnea numeric rating scale intensity of $\geq 4/10$ over the past week	Karnofsky performance status $\geq 40\%$	NR	Diagnosis of cancer with clinical or radiologic evidence of lung involvement, age 18 or older, able to communicate in English, seen at the Thoracic Medical Oncology or Supportive Care Clinics at M. D. Anderson Cancer Center. No patients with delirium, no oxygen saturation $< 90\%$ despite standard supplemental oxygen $> 6\text{L}/\text{min}$ , no allergic reactions to dexamethasone, no diagnosis of diabetes mellitus uncontrolled on oral hypoglycemic agents or insulin, no severe anemia (hemoglobin $< 7\text{g}/\text{L}$ ) not corrected prior to study enrollment, no megestrol acetate use at the time of study enrollment, no open wound that has not been healed, no infection requiring antibiotics within the past two weeks, no major surgery within the past two weeks, no absolute neutrophil count $< 1000/\text{mm}^3$ , no chronic obstructive pulmonary disease (COPD) exacerbation, no heart failure exacerbation and active or recent chronic systemic corticosteroid use ( $> 14$ days), not receiving chemotherapy or expected to start within one week of study enrollment
Hui, 2017 <sup>40</sup>	KQ4	6 minutes	RCT	Episodic dyspnea $> 3/10$ and dyspnea at rest $< 7/10$	Karnofsky performance status $\geq 50\%$	NR	Cancer patient, opioid tolerant, ambulatory with or without walking aid, not allergic to fentanyl, no history of opioid abuse, not requiring standard supplemental oxygen, Memorial Delirium Rating Scale $< 13/30$ and no contraindications to 6MWT.
Hui, 2019 <sup>41</sup>	KQ4	Not specified NR	RCT	Average intensity level over the past seven days of $\geq 3$ NRS upon significant exertion, or continuous dyspnea at rest $\leq 7$ NRS with worsening upon significant exertion	Karnofsky $\geq 50\%$	NR	Age $\geq 18$ ; diagnosis of cancer with evidence of active disease, on strong opioids with morphine equivalent daily dose (MEDD) of 80-500 mg/day for one week or more, stable regular dose over the last 24 hours, able to walk with or without walking aid, not pregnant, no allergy to fentanyl, no history of active opioid abuse within the past 12 months, no standard supplemental oxygen requirement $> 6\text{L}/\text{minute}$ , no severe anemia (hemoglobin $< 7\text{g}/\text{dL}$ ), No MDAS score $> 13/30$ , no contraindication to completing a shuttle walk test.
Kawabata, 2013 <sup>42</sup>	KQ4	NR	Retrospective cohort	NR	NR	NR	Terminally ill cancer patients treated with iOC admitted to the palliative care unit, duration more than 48 hours, no consciousness disturbance or delirium.



Author, Year	Included in KQ4	Followup	Study Design	Baseline Breathlessness Score Inclusion Criteria	Functional Status Inclusion Criteria	Life Expectancy Inclusion Criteria	Other Inclusion Criteria
Navigante, 2006 <sup>43</sup>	KQ4	48 hours	RCT	NR	ECOG 4	≤7 days	Able to provide informed consent, ≥ 18 years of age , with a documented diagnosis of terminal advanced cancer, Mini-Mental Status Exam (MMSE) > 23/30, severe dyspnea at rest, performance status of 4 (Eastern Cooperative Oncology Group), no chronic obstructive pulmonary disease with hypercapnia, no compensated congestive heart failure, no severe renal or hepatic failure, no other uncontrolled symptoms.
Navigante, 2010 <sup>44</sup>	KQ4	5 Days	RCT	NR	NR	NR	Ambulatory patients who could provide informed consent and were 18 years or older, with a documented diagnosis of advanced cancer, Mini-Mental Status Examination score >23 out of 30, moderate or severe dyspnea at rest, and a performance status of ≤3. Inactive or controlled chronic obstructive pulmonary disease (COPD), no non-compensated congestive heart failure, no severe renal or hepatic failure, and controlled symptoms (numerical rating scale [NRS] >3 out of 10), and hemoglobin saturation by pulse oximetry (SaO2) ≥85%.
Peoples, 2016 <sup>45</sup>	NR	28 days	RCT	Grade 2 or higher within past 5 days on MMRCDS	NR	NR	Outpatients with any cancer diagnosis, receiving chemotherapy, at least 18 years of age, have adequate renal, hepatic and cardiac function, not taking monoamine oxidase inhibitors, not taken any such drugs within 14 days, no history of mania or seizures, no unstable medical or psychiatric illness, no previous hypersensitivity reaction to buspirone. Patients with pleural effusions were eligible if the effusion had been drained or treated with sclerotherapy or if the effusion did not require drainage. Anemic patients were eligible if their Hgb at study entry was greater than 8gm/dl and they had not been transfused in the 15 days prior to study entry.
Pinna, 2015 <sup>46</sup>	KQ4	7 Days	RCT: Crossover	ESAS score ≥3	NR	NR	Karnofsky index score > 50, hemoglobin levels in the past month > 10 mg/dL, SaO2 >90%, and no patients with advanced chronic obstructive pulmonary disease (COPD).



Author, Year	Included in KQ4	Followup	Study Design	Baseline Breathlessness Score Inclusion Criteria	Functional Status Inclusion Criteria	Life Expectancy Inclusion Criteria	Other Inclusion Criteria
Simon, 2016 <sup>47</sup>	NR	60 minutes	RCT: Crossover	≥3 NRS score	NR	≥1 month	Adult inpatients aged 18 years or older with incurable cancer, opioid tolerant for at least one day (30-mg oral morphine, 15-mg oral oxycodone, 4-mg oral hydromorphone, 12-mg/hour transdermal fentanyl, or an analgesic equivalent of a different opioid or a different routes of application), has controlled breathlessness or performance status, no respiratory depression, no situation that impairs drug absorption, estimated glomerular filtration rate ≥25 mL/minute, no severe hepatic impairment, no opioid abuse, no use of a monoamine oxidase inhibitors, no selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors, no pregnant women or nursing mothers, no treatment with any other investigational drugs, and no participants who were unable to take the trial medication, able to give informed consent.
Tian, 2016 <sup>48</sup>	KQ4	60 minutes	Retrospective cohort	NR	NR	< 1 month	≥18 years of age, diagnosed with cancer, provided the subjective self-report of moderate-to-severe dyspnea, serum creatinine concentration within twice the normal range, undergoing medicine intervention for dyspnea, no serious renal or hepatic failure, inactive or controlled chronic obstructive pulmonary disease, no serious lung infection, not diagnosed with hemoglobin saturation by pulse oximetry <85%, no superior vena cava syndrome, no non-compensated congestive heart failure, no contraindication to morphine, benzodiazepine drugs, and hormones.

6MWT=6 minute walk test; AKPS=Australian-modified Karnofsky Performance Score; COPD= Chronic obstructive pulmonary disease; ECOG= Eastern Cooperative Oncology Group Performance Status; KQ4=Key Question 4; MEDD= morphine equivalent daily dose; MMRCDS=Modified Medical Research Council Dyspnea Scale; MMSE= Mini-Mental Status Exam; NR=not reported; NRS=numerical rating scale; RCT=randomized clinical trial; VAS=visual analog scale



**Evidence Table D-6. Inclusion criteria for studies comparing combination of non-pharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Followup	Study Design	Baseline Breathlessness Score Inclusion Criteria	Functional Status Inclusion Criteria	Life Expectancy Inclusion Criteria	Other Inclusion Criteria
Gottlieb, 2020 <sup>49</sup>	NR	25 weeks	RCT	NR	NR	NR	Lung or head and neck cancer and COPD (FEV1/FVC<0.7, no significant reversibility with beta-agonists, no asthma diagnosis)
Minchom, 2016 <sup>50</sup>	KQ4	14 days	RCT	VAS ≥4	Eastern Cooperative Oncology Group performance status (PS) 0-3	NR	Non-small cell lung cancer (NSCLC) or mesothelioma, no change in treatment (chemotherapy/radiotherapy) in the previous 4 weeks, no change of steroids in the previous 1 week, no acupuncture in the previous 4 weeks, no acupuncture contraindications, no current morphine use or reversible causes of breathlessness.

COPD=Chronic obstructive pulmonary disease; KQ4=Key Question 4; NR=not reported; NSCLC= Non-small cell lung cancer; PS=performance status; RCT=randomized clinical trial; VAS=Visual Analog Scale



Evidence Table D-7. Participant demographic characteristics for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients										
Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Booth, 1996 <sup>1</sup>	NR	Overall	All patients	38	Chronic	Chronic: 38 (100) Exertional: NR Other breathlessness: NR	NR	Male: 22 (58) Female: 16 (42)	Mean (SD): NR Median: 71 Range: 54- 90	NR
Bordeleau, 2003 <sup>2</sup>	KQ4	Arm 1	Control	70	Chronic	NR	ECOG n (%): ECOG 0=17, ECOG 1- 40, ECOG 2= 13 (ECOG 0=24, ECOG 1= 57, ECOG 2= 19) Mean (SD): NR Median: NR Range: NR	Male: 0 (0) Female: 70 (100)	Mean (SD): 51.5 (10) Median: NR Range: NR	NR
Bordeleau, 2003 <sup>2</sup>	KQ4	Arm 2	Intervention	145	Chronic	NR	ECOG n (%): ECOG 0= 48, ECOG 1= 72, ECOG 2= 25 (ECOG 0=33, ECOG 1= 50, ECOG 2= 17) Mean (SD): NR Median: NR Range: NR	Male: 0 (0) Female: 145 (100)	Mean (SD): 49.4 (8.4) Median: NR Range: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Bruera, 1993 <sup>3</sup>	NR	Overall	All patients	14	Chronic	NR	NR	Male: 8 (57) Female: 6 (43)	Mean (SD): NR Median: 64 Range: 49- 79	NR
Bruera, 2003 <sup>4</sup>	KQ4	Overall	All patients	33	Chronic	NR	NR	Male: 21 (64) Female: 12 (36)	Mean (SD): NR Median: 64 Range: 41- 79	NR
Chan, 2011 <sup>5</sup>	KQ4	Overall	All patients	140	Chronic	NR	Karnofsky n (%): NR Mean (SD): 84 (NR) Median: NR Range: NR	Male: 116 (0.83) Female: 24 (0.17)	Mean (SD): NR Median: NR Range: NR	NR
Corner, 1996 <sup>6</sup>	KQ4	Arm 1	Control	9	Chronic	NR	NR	Male: 7 (78) Female: 2 (22)	Mean (SD): NR Median: 69 Range: NR	NR
Corner, 1996 <sup>6</sup>	KQ4	Arm 2	Nurse led intervention	11	Chronic	NR	NR	Male: 5 (46) Female: 6 (54)	Mean (SD): NR Median: 55 Range: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Dhillon, 2017 <sup>7</sup>	KQ4	Arm 1	Usual care	55	Chronic	NR	ECOG n (%): 0= 32 (58), 1= 21 (38), 2= 2 (4) Mean (SD): NR Median: NR Range: NR	Male: 32 (58) Female: 23 (42)	Mean (SD): NR Median: 64 Range: 34 to 76	NR
Dhillon, 2017 <sup>7</sup>	KQ4	Arm 2	Exercise	56	Chronic	NR	ECOG n (%): 0= 29 (52), 1 = 25 (45), 2= 2 (4) Mean (SD): NR Median: NR Range: NR	Male: 29 (52) Female: 27 (48)	Mean (SD): NR Median: 64 Range: 38 to 80	NR
Dogan, 2019 <sup>8</sup>	KQ4	Arm 1	Control	31	Chronic	NR	NR	Male: 29 (94) Female: 2 (6)	Mean (SD): 63.1 (8) Median: NR Range: NR	NR
Dogan, 2019 <sup>8</sup>	KQ4	Arm 2	Acupressure	29	Chronic	NR	NR	Male: 24 (83) Female: 5 (17)	Mean (SD): 59 (8.1) Median: NR Range: NR	NR
Farquhar, 2014 <sup>9</sup>	KQ4	Arm 1	Control	32	Chronic	NR	Australia-modified Karnofsky Performance Scale n (%): NR Mean (SD): 74.1 (14.8) Median: NR Range: NR	Male: 12 (38) Female: 20 (62)	Mean (SD): 67 (13.3) Median: NR Range: NR	NR
Farquhar, 2014 <sup>9</sup>	KQ4	Arm 2	Intervention	35	Chronic	NR	Australia-modified Karnofsky Performance Scale n (%): NR Mean (SD): 71.1 (12.6) Median: NR Range: NR	Male: 14 (41) Female: 21 (59)	Mean (SD): 70 (9.4) Median: NR Range: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Henke, 2014 <sup>10</sup>	KQ4	Arm 1	Control	11	Chronic	NR	NR	Male: NR Female: NR	Mean (SD): NR Median: NR Range: NR	NR
Henke, 2014 <sup>10</sup>	KQ4	Arm 2	Intervention	18	Chronic	NR	NR	Male: NR Female: NR	Mean (SD): NR Median: NR Range: NR	NR
Hui, 2013 <sup>11</sup>	KQ4	Overall	All patients	30	Chronic	Chronic: 30 (100) Exertional: NR Other breathlessness: NR	ECOG n (%): 3=27, 4=3 (3=90, 4=10) Mean (SD): NR Median: NR Range: NR	Male: 14 (47) Female: 16 (53)	Mean (SD): 61 (NR) Median: NR Range: 29-79	White: 23 (77) Black: 6 (20) Hispanic: 1 (3) Asian: 0 (0) Other: 0 (0)
Hui, 2013 <sup>11</sup>	KQ4	Arm 1	Bilevel positive airway pressure (BiPAP)	14	Chronic	Chronic: 14 (100) Exertional: NR Other breathlessness: NR	ECOG n (%): 3=13, 4=1 (3=93, 4=7) Mean (SD): NR Median: NR Range: NR	Male: 8 (57) Female: 6 (43)	Mean (SD): 63 (NR) Median: NR Range: 47-79	White: 11 (79) Black: 3 (21) Hispanic: 0 (0) Asian: 0 (0) Other: 0 (0)
Hui, 2013 <sup>11</sup>	KQ4	Arm 2	High flow nasal cannula	16	Chronic	Chronic: 16 (100) Exertional: NR Other breathlessness: NR	ECOG n (%): 3=14, 4=2 (3=88, 4=12) Mean (SD): NR Median: NR Range: NR	Male: 6 (37) Female: 10 (63)	Mean (SD): 59 (NR) Median: NR Range: 29-79	White: 12 (75) Black: 3 (19) Hispanic: 1 (6) Asian: 0 (0) Other: 0 (0)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Hwang, 2012 <sup>12</sup>	NR	Arm 1	Control	11	Chronic	NR	NR	Male: 7 (64) Female: 4 (36)	Mean (SD): 58.5 (8.2) Median: NR Range: NR	NR
Hwang, 2012 <sup>12</sup>	NR	Arm 2	Exercise	13	Chronic	NR	NR	Male: 5 (39) Female: 8 (61)	Mean (SD): 61 (6.3) Median: NR Range: NR	NR
Kako, 2018 <sup>13</sup>	NR	Arm 1	Fan to legs (control)	20	Chronic	Chronic: 20 (100) Exertional: NR Other breathlessness: NR	ECOG, KPS n (%): ECOG 3= 15, ECOG 4= 5, KPS mean (SD) 43 (7.3) (75, 25) Mean (SD): NR Median: NR Range: NR	Male: 10 (50) Female: 10 (50)	Mean (SD): 67 (11.9) Median: NR Range: NR	NR
Kako, 2018 <sup>13</sup>	NR	Arm 2	Fan to face	20	Chronic	Chronic: 20 (100) Exertional: NR Other breathlessness: NR	ECOG, KPS n (%): ECOG 3= 16, ECOG 4= 4, KPS mean (SD) 42.5 (10.7) (80, 20) Mean (SD): NR Median: NR Range: NR	Male: 12 (60) Female: 8 (40)	Mean (SD): 71.5 (8.2) Median: NR Range: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Ligibel, 2016 <sup>14</sup>	NR	Arm 1	Control	51	Chronic	NR	ECOG n (%): 0= 38 (74), 1= 12 (24) Mean (SD): NR Median: NR Range: NR	Male: 0 (0) Female: 51 (100)	Mean (SD): 50.7 (9.4) Median: NR Range: NR	White: 45 (88) Black: 5 (10) Hispanic: NR Asian: 1 (2) Other: NR
Ligibel, 2016 <sup>14</sup>	NR	Arm 2	Exercise	47	Chronic	NR	ECOG n (%): 0= 38 (81), 1= 8 (17) Mean (SD): NR Median: NR Range: NR	Male: 0 (0) Female: 47 (100)	Mean (SD): 49.3 (9.6) Median: NR Range: NR	White: 47 (100) Black: 0 (0) Hispanic: NR Asian: 0 (0) Other: NR
McMillan, 2007 <sup>15</sup>	KQ4	Arm 1	Standard care	109	Chronic	NR	PPS n (%): NR Mean (SD): 51.42 (NR) Median: 9.96 Range: NR	Male: 61 (56) Female: 48 (44)	Mean (SD): 70.12 (12.58) Median: NR Range: NR	NR
McMillan, 2007 <sup>15</sup>	KQ4	Arm 2	Standard care and support	108	Chronic	NR	PPS n (%): NR Mean (SD): 52.57 (NR) Median: 11.09 Range: NR	Male: 66 (61) Female: 42 (39)	Mean (SD): 71.02 (12.12) Median: NR Range: NR	NR
McMillan, 2007 <sup>15</sup>	KQ4	Arm 3	Standard care and COPE	111	Chronic	NR	PPS n (%): NR Mean (SD): 54.5 (NR) Median: 7.88 Range: NR	Male: 70 (63) Female: 41 (37)	Mean (SD): 70.84 (10.99) Median: NR Range: NR	NR
Molassiotis, 2015 <sup>16</sup>	KQ4	Overall	All patients	46	Chronic	Chronic: NR Exertional: NR Other breathlessness: 46 (100)	NR	Male: 37 (80) Female: 9 (20)	Mean (SD): 69.5 (8.35) Median: NR Range: 51-85	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Moore, 2002 <sup>17</sup>	KQ4	Arm 1	Control	103	Chronic	NR	WHO n (%): WHO 0= 4, 1=64, 2=35 (WHO 0= 4, 1=62, 2=34) Mean (SD): NR Median: NR Range: NR	Male: 66 (64) Female: 37 (36)	Mean (SD): 67 (8.8) Median: NR Range: 45-89	NR
Moore, 2002 <sup>17</sup>	KQ4	Arm 2	Nurse-led intervention	99	Chronic	NR	WHO n (%): WHO 0= 8, 1=59, 2=32 (WHO 0= 8, 1=60, 2=32) Mean (SD): NR Median: NR Range: NR	Male: 74 (75) Female: 25 (25)	Mean (SD): 67 (8.8) Median: NR Range: 45-89	NR
Mosher, 2019 <sup>18</sup>	KQ4	Arm 1	Education/ support	25	Chronic	Chronic: NR Exertional: NR Other breathlessness: 13 (52)	ECOG n (%): NR Mean (SD): 1 (0.66) Median: NR Range: 0-2	Male: 14 (56) Female: 11 (44)	Mean (SD): 62 (13.13) Median: NR Range: 37- 82	White: 23 (92) Black: NR Hispanic: NR Asian: NR Other: NR
Mosher, 2019 <sup>18</sup>	KQ4	Arm 2	Acceptance and Commitment Therapy (ACT)	25	Chronic	Chronic: NR Exertional: NR Other breathlessness: 15 (60)	ECOG n (%): NR Mean (SD): 0.96 (0.69) Median: NR Range: 0-2	Male: 14 (56) Female: 11 (44)	Mean (SD): 63.2 (11.27) Median: NR Range: 35- 81	White: 20 (80) Black: NR Hispanic: NR Asian: NR Other: NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Nakano, 2020 <sup>19</sup>	NR	Overall	Overall	20	Chronic	NR	ECOG n (%): 2= 5 (25) , 3= 12 (60), 4= 3 (15) Mean (SD): NR Median: NR Range: NR	Male: 17 (85) Female: 3 (15)	Mean (SD): 70 (6.3) Median: NR Range: NR	NR
Nava, 2013 <sup>20</sup>	KQ4	Arm 1	Noninvasive ventilation (NIV)	99	NR	At rest: 99 (100) Exertional: NR Other breathlessness: NR	NR	Male: 59 (59) Female: 40 (40)	Mean (SD): 71 (11) Median: NR Range: NR	NR
Nava, 2013 <sup>20</sup>	KQ4	Arm 2	Oxygen	101	NR	NR	NR	Male: 65 (65) Female: 36 (36)	Mean (SD): 70 (12) Median: NR Range: NR	NR
Philip, 2006 <sup>21</sup>	NR	Overall	All patients	51	Chronic	Chronic: 51 (100) Exertional: NR Other breathlessness: NR	ECOG n (%): 2=13, 3=37, 4= 1 (25, 73, 2) Mean (SD): NR Median: NR Range: NR	Male: 31 (61) Female: 20 (39)	Mean (SD): NR Median: 65 Range: 33- 82	NR
Philip, 2006 <sup>21</sup>	NR	Arm 1	Air first	27	Chronic	Chronic: 27 (100) Exertional: NR Other breathlessness: NR	ECOG n (%): 2=7, 3= 19, 4= 1 (26, 70, 4) Mean (SD): NR Median: NR Range: NR	Male: 19 (70) Female: 8 (30)	Mean (SD): NR Median: 65 Range: 33-81	NR
Philip, 2006 <sup>21</sup>	NR	Arm 2	Oxygen first	24	Chronic	Chronic: 24 (100) Exertional: NR Other breathlessness: NR	ECOG n (%): 2=6, 3= 18, 4= 0 (25, 75, 0) Mean (SD): NR Median: NR Range: NR	Male: 12 (50) Female: 12 (50)	Mean (SD): NR Median: 64 Range: 37- 82	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Ramirez, 2018 <sup>22</sup>	NR	Overall	All patients	40	NR	NR	NR	Male: 27 (68) Female: 13 (32)	Mean (SD): 69 (15) Median: NR Range: NR	NR
Rutkowska, 2019 <sup>23</sup>	NR	Arm 1	Control	10	Chronic	NR	WHO n (%): 0=1 (10), 1= 9 (90) Mean (SD): NR Median: NR Range: NR	Male: 9 (90) Female: 1 (10)	Mean (SD): 61.3 (8.8) Median: NR Range: NR	NR
Rutkowska, 2019 <sup>23</sup>	NR	Arm 2	Exercise	20	Chronic	NR	WHO n (%): 0= 3 (15), 1 =17 (85) Mean (SD): NR Median: NR Range: NR	Male: 18 (90) Female: 2 (10)	Mean (SD): 59.1 (6.8) Median: NR Range: NR	NR
Ting, 2020 <sup>24</sup>	NR	Arm 1	Group A (of crossover, does not correspond to drug arms)	24	Chronic	NR	ECOG 3=12 (50), 4=12 (50)	Male: 9 (38) Female: 15 (62)	Mean (SD): 52.2 (SD 20) Median: NR Range: NR	NR
Ting, 2020 <sup>24</sup>	NR	Arm 2	Group B (of crossover, does not correspond to drug arms)	24	Chronic	NR	ECOG 3=13 (54), 4=11 (46)	Male: 13 (54) Female: 11 (46)	Mean (SD): 49.8 (SD 16.3) Median: NR Range: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Vanderbyl, 2017 <sup>25</sup>	KQ4	Arm 1	Standard exercise therapy	13	Chronic	NR	ECOG n (%): 0=2, 1=11 (15.85) Mean (SD): NR Median: NR Range: NR	Male: 7 (54) Female: 6 (46)	Mean (SD): 63.7 (7.7) Median: NR Range: NR	NR
Vanderbyl, 2017 <sup>25</sup>	KQ4	Arm 2	Qigong	11	Chronic	NR	ECOG n (%): 0=1, 2=10 (9, 91) Mean (SD): NR Median: NR Range: NR	Male: 7 (64) Female: 4 (36)	Mean (SD): 66.1 (11.7) Median: NR Range: NR	NR
Vickers, 2005 <sup>26</sup>	KQ4	Arm 1	Control	20	Chronic	Chronic: 6 (30) Exertional: NR Other breathlessness: NR	NR	Male: 7 (35) Female: 13 (65)	Mean (SD): 67 (11.4) Median: NR Range: NR	NR
Vickers, 2005 <sup>26</sup>	KQ4	Arm 2	Acupuncture/acupressure	25	Chronic	Chronic: 9 (36) Exertional: NR Other breathlessness: NR	NR	Male: 10 (40) Female: 15 (60)	Mean (SD): 63 (12.8) Median: NR Range: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Wong, 2017 <sup>27</sup>	NR	Arm 1	Control	15	Chronic	Chronic: 15 (100) Exertional: NR Other breathlessness: NR	NR	Male: 8 (53) Female: 7 (47)	Mean (SD): (NR) Median: NR Range: NR	NR
Wong, 2017 <sup>27</sup>	NR	Arm 2	Fan	15	Chronic	Chronic: 15 (100) Exertional: NR Other breathlessness: NR	NR	Male: 6 (40) Female: 9 (60)	Mean (SD): (NR) Median: NR Range: NR	NR
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 1	Control	96	Chronic	NR	NR	Male: 0 (0) Female: 96 (100)	Mean (SD): 57.3 (11.8) Median: NR Range: NR	White: 83 (86) Black: NR Hispanic: NR Asian: NR Other: 13 (14)
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 2	Lay foot manipulation	95	Chronic	NR	NR	Male: 0 (0) Female: 95 (100)	Mean (SD): 54.8 (11.2) Median: NR Range: NR	White: 75 (79) Black: NR Hispanic: NR Asian: NR Other: 20 (21)
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 3	Reflexology	95	Chronic	NR	NR	Male: 0 (0) Female: 95 (100)	Mean (SD): 55.3 (9.4) Median: NR Range: NR	White: 80 (84) Black: NR Hispanic: NR Asian: NR Other: 15 (16)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Yorke, 2015 <sup>29</sup>	KQ4	Arm 1	Usual care	51	Chronic	At rest: NR Exertional: NR Other breathlessness: 50 (98)	Other-specify n (%): 1=21, 2=19 (1=53, 2=47) Mean (SD): NR Median: NR Range: NR	Male: 25 (49) Female: 26 (51)	Mean (SD): 67.6 (9.1) Median: NR Range: NR	NR
Yorke, 2015 <sup>29</sup>	KQ4	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	50	Chronic	At rest: NR Exertional: NR Other breathlessness: 48 (96)	Other-specify n (%): 1=25, 2=16 (1=61, 2=39) Mean (SD): NR Median: NR Range: NR	Male: 22 (44) Female: 28 (56)	Mean (SD): 67.8 (10.1) Median: NR Range: NR	NR

BiPAP= Bilevel positive airway pressure; ECOG= Eastern Cooperative Oncology Group Performance Status; KPS= Karnofsky Performance Score; KQ4=Key Question 4; n=population; NR=not reported; PPS= Palliative Performance Scale; SD=standard deviation; WHO=World Health Organization



**Evidence Table D-8. Participant cancer and comorbidity characteristics for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Booth, 1996 <sup>1</sup>	NR	Overall	All patients	38	Lung, mesothelioma, others	Lung/Mesothelioma: 22 (58) Non-lung/mesothelioma: 16 (42)	Advanced: 38 (100)	NR	Opioids: 27 (71), Benzos: 20 (53)	COPD: 13 (34) Heart failure: 4 (11) Asthma: NR
Bordeleau, 2003 <sup>2</sup>	KQ4	Arm 1	Control	70	Breast	Lung/Mesothelioma: 0 (0) Non-lung/mesothelioma: 70 (100)	Metastatic: 70 (100)	Both, Chemotherapy, hormonal therapy, radiotherapy Systemic: 59 (83) Local: 5 (7)	NR	NR
Bordeleau, 2003 <sup>2</sup>	KQ4	Arm 2	Intervention	145	Breast	Lung/Mesothelioma: 0 (0) Non-lung/mesothelioma: 145 (100)	Metastatic: 145 (100)	Both, Chemotherapy, hormonal therapy, radiotherapy Systemic: 120 (83) Local: 5 (3)	NR	NR
Bruera, 1993 <sup>3</sup>	NR	Overall	All patients	14	Lung, other	Lung/Mesothelioma: 5 (36) Non-lung/mesothelioma: 9 (64)	Advanced: 14 (100)	NR	NR	COPD: 0 (0) Heart failure: NR Asthma: NR
Bruera, 2003 <sup>4</sup>	KQ4	Overall	All patients	33	Lung, other	Lung/Mesothelioma: 31 (94) Non-lung/mesothelioma: 2 (6)	Locally advanced and metastatic: 33 (100)	NR	NR	COPD: NR Heart failure: NR Asthma: NR
Chan, 2011 <sup>5</sup>	KQ4	Overall	All patients	140	Lung	Lung/Mesothelioma: 140 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 140 (100)	Both, Chemotherapy + radiotherapy Systemic: 25 (18) Local: 140 (100)	NR	COPD: NR Heart failure: NR Asthma: NR "Comorbidity": 56 (0.4)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Corner, 1996 <sup>6</sup>	KQ4	Arm 1	Control	9	Lung	Lung/Mesothelioma: 9 (100) Non-lung/mesothelioma: 0 (0)	Advanced: 9 (100)	NR	NR	NR
Corner, 1996 <sup>6</sup>	KQ4	Arm 2	Nurse led intervention	11	Lung	Lung/Mesothelioma: 11 (100) Non-lung/mesothelioma: 0 (0)	Advanced: 11 (100)	NR	NR	NR
Dhillon, 2017 <sup>7</sup>	KQ4	Arm 1	Usual care	55	Lung	Lung/Mesothelioma: 55 (100) Non-lung/mesothelioma: 0 (0)	Locally advanced and metastatic: 55 (100)	Chemotherapy and targeted therapy Systemic: 43 (0.78) Local: 0 (0)	NR	NR
Dhillon, 2017 <sup>7</sup>	KQ4	Arm 2	Exercise	56	Lung	Lung/Mesothelioma: 56 (100) Non-lung/mesothelioma: 0 (0)	Locally advanced and metastatic: 56 (100)	Chemotherapy and targeted therapy Systemic: 44 (0.79) Local: 0 (0)	NR	NR
Dogan, 2019 <sup>8</sup>	KQ4	Arm 1	Control	31	Lung	Lung/Mesothelioma: 31 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 30 (97)	Systemic, Chemotherapy alone: 31 (100)	NR	COPD: 0 (0) Heart failure: 0 (0) Asthma: 0 (0)
Dogan, 2019 <sup>8</sup>	KQ4	Arm 2	Acupressure	29	Lung	Lung/Mesothelioma: 29 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 28 (97)	Systemic, Chemotherapy alone: 29 (100)	NR	COPD: 0 (0) Heart failure: 0 (0) Asthma: 0 (0)
Farquhar, 2014 <sup>9</sup>	KQ4	Arm 1	Control	32	Lung, mesothelioma, breast, GI, GU, lymphoma, others	Lung/Mesothelioma: 19 (60) Non-lung/mesothelioma: 13 (40)	Advanced: 32 (100)	NR	NR	NR
Farquhar, 2014 <sup>9</sup>	KQ4	Arm 2	Intervention	35	Lung, mesothelioma, breast, GI, GU, lymphoma, others	Lung/Mesothelioma: 17 (48) Non-lung/mesothelioma: 18 (52)	Advanced: 35 (100)	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Henke, 2014 <sup>10</sup>	KQ4	Arm 1	Control	11	Lung	Lung/Mesothelioma: 11 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 11 (100)	Systemic, Chemotherapy Systemic: 11 (100) Local: NR	NR	NR
Henke, 2014 <sup>10</sup>	KQ4	Arm 2	Intervention	18	Lung	Lung/Mesothelioma: 18 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 18 (100)	Systemic, Chemotherapy Systemic: 18 (100) Local: NR	NR	NR
Hui, 2013 <sup>11</sup>	KQ4	Overall	All patients	30	Breast, GI, GU, Head and neck, lung, other	Lung/Mesothelioma: 13 (43) Non-lung/mesothelioma: 17 (57)	Locally advanced and metastatic: 30 (100)	NR	Opioids: 27 (82), Steroids: 17 (59), Oxygen: 26 (93)	COPD: 10 (33) Heart failure: 1 (3) Asthma: 1 (3)
Hui, 2013 <sup>11</sup>	KQ4	Arm 1	Bilevel positive airway pressure (BiPAP)	14	Breast, GI, GU, Head and neck, lung, other	Lung/Mesothelioma: 6 (43) Non-lung/mesothelioma: 8 (57)	Locally advanced and metastatic: 14 (100)	NR	Opioids: 12 (92), Steroids: 7 (54), Oxygen: 14 (100)	COPD: 5 (36) Heart failure: 0 (0) Asthma: 1 (7)
Hui, 2013 <sup>11</sup>	KQ4	Arm 2	High flow nasal cannula	16	Breast, GI, GU, Head and neck, lung, other	Lung/Mesothelioma: 7 (44) Non-lung/mesothelioma: 9 (56)	Locally advanced and metastatic: 16 (100)	NR	Opioids: 15 (94), Steroids: 10 (63), Oxygen: 12 (86)	COPD: 5 (31) Heart failure: 1 (6) Asthma: 0 (0)
Hwang, 2012 <sup>12</sup>	NR	Arm 1	Control	11	Lung	Lung/Mesothelioma: 11 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 11 (100)	Systemic, Targeted therapy Systemic: 11 (100) Local: NR	NR	COPD: 0 (0) Heart failure: NR Asthma: NR
Hwang, 2012 <sup>12</sup>	NR	Arm 2	Exercise	13	Lung	Lung/Mesothelioma: 13 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 13 (100)	Systemic, Targeted therapy Systemic: 13 (100) Local: NR	NR	COPD: 0 (0) Heart failure: NR Asthma: NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Kako, 2018 <sup>13</sup>	NR	Arm 1	Fan to legs (control)	20	Lung, colorectal, breast, stomach, esophagus, gallbladder/bili duct, pancreas, head and neck, prostate	Lung/Mesothelioma: 4 (20) Non-lung/mesothelioma: 16 (80)	Metastatic or locally advanced: 20 (100)	NR	Opioids: 15 (75), Steroids: 8 (40), Benzos: 4 (20), Oxygen: 11 (55)	COPD: 2 (10) Heart failure: 1 (5) Asthma: 0 (0) ILD: 1 (5)
Kako, 2018 <sup>13</sup>	NR	Arm 2	Fan to face	20	Lung, colorectal, breast, stomach, esophagus, gallbladder/bili duct, liver, uterus/ ovary, skin, unknown	Lung/Mesothelioma: 11 (55) Non-lung/mesothelioma: 9 (45)	Metastatic or locally advanced: 20 (100)	NR	Opioids: 14 (70), Steroids: 9 (45), Benzos: 1 (5), Oxygen: 9 (45)	COPD: 4 (20) Heart failure: 2 (10) Asthma: 0 (0) ILD: 2 (10)
Ligibel, 2016 <sup>14</sup>	NR	Arm 1	Control	51	Breast	Lung/Mesothelioma: 0 (0) Non-lung/mesothelioma: 51 (100)	Locally advanced and metastatic: 51 (100)	Chemotherapy, hormone therapy, targeted therapy Systemic: 50 (0.98) Local: 0 (0)	NR	NR
Ligibel, 2016 <sup>14</sup>	NR	Arm 2	Exercise	47	Breast	Lung/Mesothelioma: 0 (0) Non-lung/mesothelioma: 47 (100)	Locally advanced and metastatic: 47 (100)	Chemotherapy, hormone therapy, targeted therapy Systemic: 45 (0.96) Local: 0 (0)	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
McMillan, 2007 <sup>15</sup>	KQ4	Arm 1	Standard care	109	NR	NR	'Hospice': 109 (100)	NR	NR	NR
McMillan, 2007 <sup>15</sup>	KQ4	Arm 2	Standard care and support	108	NR	NR	'Hospice': 109 (100)	NR	NR	NR
McMillan, 2007 <sup>15</sup>	KQ4	Arm 3	Standard care and COPE	111	NR	NR	'Hospice': 111 (100)	NR	NR	NR
Molassiotis, 2015 <sup>16</sup>	KQ4	Overall	All patients	46	Lung, mesothelioma	Lung/Mesothelioma: 46 (100) Non-lung/mesothelioma: 0 (0)	Stage 1, 2, 3, 4, unknown: 27 (59)	NR	Opioids: 5 (11), Steroids: 13 (28), Oxygen: 15 (33)	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Moore, 2002 <sup>17</sup>	KQ4	Arm 1	Control	103	Lung, mesothelioma	Lung/Mesothelioma: 103 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 89 (88)	NR	NR	COPD: 9 (9) Heart failure: 16 (16) Asthma: NR
Moore, 2002 <sup>17</sup>	KQ4	Arm 2	Nurse-led intervention	99	Lung, mesothelioma	Lung/Mesothelioma: 99 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 83 (83)	NR	NR	COPD: 8 (8) Heart failure: 29 (29) Asthma: NR
Mosher, 2019 <sup>18</sup>	KQ4	Arm 1	Education/support	25	Lung	Lung/Mesothelioma: 25 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 25 (100)	NR	NR	NR
Mosher, 2019 <sup>18</sup>	KQ4	Arm 2	Acceptance and Commitment Therapy (ACT)	25	Lung	Lung/Mesothelioma: 25 (100) Non-lung/mesothelioma: 0 (0)	Stage 3, 4: 25 (100)	NR	NR	NR
Nakano, 2020 <sup>19</sup>	NR	Overall	Overall	20	Lung, gastrointestinal, genitourinary, head and neck, breast. Lymphoma	Lung/Mesothelioma: 1 (5) Non-lung/mesothelioma: 19 (20)	Stage III and IV: III: 17 (85); IV: 3 (15)	Chemotherapy + radiotherapy Systemic: 18 (0.9) Local: 14 (70)	NR	NR
Nava, 2013 <sup>20</sup>	KQ4	Arm 1	Noninvasive ventilation (NIV)	99	Lung, GI, breast, head and neck, other	Lung/Mesothelioma: 38 (38) Non-lung/mesothelioma: 61 (61)	End-stage: 99 (100)	NR	NR	NR
Nava, 2013 <sup>20</sup>	KQ4	Arm 2	Oxygen	101	Lung, GI, breast, head and neck, other	Lung/Mesothelioma: 42 (42) Non-lung/mesothelioma: 59 (59)	End-stage: 101 (100)	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Philip, 2006 <sup>21</sup>	NR	Overall	All patients	51	Lung, breast, colon, others	Lung/Mesothelioma: 28 (55) Non-lung/mesothelioma: 23 (45)	Advanced: 51 (100)	NR	NR	COPD: 11 (22) Heart failure: NR Asthma: NR
Philip, 2006 <sup>21</sup>	NR	Arm 1	Air first	27	Lung, breast, colon, others	Lung/Mesothelioma: 17 (63) Non-lung/mesothelioma: 10 (37)	Advanced: 27 (100)	NR	NR	NR
Philip, 2006 <sup>21</sup>	NR	Arm 2	Oxygen first	24	Lung, breast, colon, others	Lung/Mesothelioma: 11 (46) Non-lung/mesothelioma: 13 (54)	Advanced: 24 (100)	NR	NR	NR
Ramirez, 2018 <sup>22</sup>	NR	Overall	All patients	40	NR	NR	Advanced: 40 (100)	NR	NR	NR
Rutkowska, 2019 <sup>23</sup>	NR	Arm 1	Control	10	Lung	Lung/Mesothelioma: 10 (100) Non-lung/mesothelioma: 0 (0)	Locally advanced and metastatic: 10 (100)	Chemotherapy alone Systemic: 10 (1) Local: 0 (0)	NR	COPD: 5 (50) Heart failure: 0 (0) Asthma: NR Other, Diabetes mellitus: 3 (30)
Rutkowska, 2019 <sup>23</sup>	NR	Arm 2	Exercise	20	Lung	Lung/Mesothelioma: 20 (100) Non-lung/mesothelioma: 0 (0)	Locally advanced and metastatic: 20 (100)	Chemotherapy alone Systemic: 20 (1) Local: 0 (0)	NR	COPD: 12 (60) Heart failure: 0 (0) Asthma: NR Other, Diabetes mellitus: 6 (30)
Vanderbyl, 2017 <sup>25</sup>	KQ4	Arm 1	Standard exercise therapy	13	Lung, GI	Lung/Mesothelioma: 5 (38) Non-lung/mesothelioma: 8 (62)	Stage 3, 4: 13 (100)	Systemic, Chemotherapy Systemic: 9 (69) Local: NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Ting, 2020 <sup>24</sup>	NR	Arm 1	Group A (of crossover, does not correspond to drug arms)	24	Lung, gastrointestinal, genitourinary, head and neck, breast, lymphoma, melanoma, sarcoma	Lung/Mesothelioma: 7 (29) Non-lung/mesothelioma: 17 (71)	Locally advanced and metastatic: 24 (100)	NR	NR	COPD: 1 (4) Heart failure: NR Asthma: NR Other, Pneumonia: 16 (67)
Ting, 2020 <sup>24</sup>	NR	Arm 2	Group B (of crossover, does not correspond to drug arms)	24	Lung, gastrointestinal, genitourinary, head and neck, breast, lymphoma, melanoma, sarcoma	Lung/Mesothelioma: 3 (13) Non-lung/mesothelioma: 21 (81)	Locally advanced and metastatic: 24 (100)	NR	NR	COPD: 2 (8) Heart failure: NR Asthma: NR Other, Pneumonia: 17 (71)
Vanderbyl, 2017 <sup>25</sup>	KQ4	Arm 2	Qigong	11	Lung, GI	Lung/Mesothelioma: 7 (64) Non-lung/mesothelioma: 4 (36)	Stage 3, 4: 11 (100)	Systemic, Chemotherapy, targeted therapy Systemic: 8 (73) Local: NR	NR	NR
Vickers, 2005 <sup>26</sup>	KQ4	Arm 1	Control	20	Breast, lung	Lung/Mesothelioma: 16 (80) Non-lung/mesothelioma: 4 (20)	Advanced: 20 (100)	NR	Opioids: 3 (16), Steroids: 10 (53), Diuretic: 0 (0), Bronchodilator: 7 (37)	COPD: NR Heart failure: NR Asthma: 0 (0)
Vickers, 2005 <sup>26</sup>	KQ4	Arm 2	Acupuncture/acupressure	25	Breast, lung	Lung/Mesothelioma: 20 (80) Non-lung/mesothelioma: 5 (20)	Advanced: 25 (100)	NR	Opioids: 5 (10), Steroids: 10 (40), Diuretic: 3 (12), Bronchodilator: 12 (48)	COPD: NR Heart failure: NR Asthma: 0 (0)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Wong, 2017 <sup>27</sup>	NR	Arm 1	Control	15	Lung, colon, stomach, lymphoma, breast, prostate	Lung/Mesothelioma: 7 (47) Non-lung/mesothelioma: 8 (53)	Locally advanced and metastatic: 15 (100)	NR	Standard supplemental oxygen: 14 (94)	NR
Wong, 2017 <sup>27</sup>	NR	Arm 2	Fan	15	Lung, colon, stomach, lymphoma, breast, prostate	Lung/Mesothelioma: 6 (40) Non-lung/mesothelioma: 9 (60)	Locally advanced and metastatic: 15 (100)	NR	Standard supplemental oxygen: 15 (100)	NR
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 1	Control	96	Breast	Lung/Mesothelioma: 0 (0) Non-lung/mesothelioma: 96 (100)	Stage 3, 4, recurrent, metastatic: 96 (100)	Systemic, Chemo and/ or hormonal therapy Systemic: 96 (100) Local: NR	NR	NR
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 2	Lay foot manipulation	95	Breast	Lung/Mesothelioma: 0 (0) Non-lung/mesothelioma: 95 (100)	Stage 3, 4, recurrent, metastatic: 95 (100)	Systemic, Chemo and/ or hormonal therapy Systemic: 95 (100) Local: NR	NR	NR
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 3	Reflexology	95	Breast	Lung/Mesothelioma: 0 (0) Non-lung/mesothelioma: 95 (100)	Stage 3, 4, recurrent, metastatic: 95 (100)	Systemic, Chemo and/ or hormonal therapy Systemic: 95 (100) Local: NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Yorke, 2015 <sup>29</sup>	KQ4	Arm 1	Usual care	51	Lung	Lung/Mesothelioma: 51 (100) Non-lung/mesothelioma: 0 (0)	Either cured, or on palliative therapy, or incurable and on no anticancer therapy: 33 (66)	Systemic, Palliative cancer therapy Systemic: 26 (51) Local: NR	Opioids: 18 (37), Benzos: 2 (4)	COPD: 25 (50) Heart failure: NR Asthma: NR
Yorke, 2015 <sup>29</sup>	KQ4	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	50	Lung	Lung/Mesothelioma: 50 (100) Non-lung/mesothelioma: 0 (0)	Either cured, or on palliative therapy, or incurable and on no anticancer therapy: 31 (62)	Systemic, Palliative cancer therapy Systemic: 26 (52) Local: NR	Opioids: 16 (32), Benzos: 3 (6)	COPD: 14 (28) Heart failure: NR Asthma: NR

COPD= Chronic obstructive pulmonary disease; GI=gastrointestinal; GU= genitourinary tract; ILD=interstitial lung disease; KQ4=Key Question 4; n=population; NR=not reported



**Evidence Table D-9. Participant demographic characteristics for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Aabom, 2019 <sup>30</sup>	NR	Overall	Overall	12	Exertional	At rest: NR Exertional: 12 (100) Other breathlessness: NR	ECOG n (%): 1: 8 (66.67), 2: 4 (33.33) Mean (SD): NR Median: NR Range: NR	Male: 9 (75) Female: 3 (25)	Mean (SD): 74.8 (NR) Range: 64-88	NR
Allard, 1999 <sup>31</sup>	NR	Overall	Overall	33	At rest	Chronic: 33 (100) Exertional: NR Other breathlessness: NR	NR	Male: 14 (42.4) Female: 19 (57.6)	Mean (SD): 63.3 (NR) Median: 66 Range: NR	NR
Allard, 1999 <sup>31</sup>	NR	Arm 1	Opioid dose 25% of 4 hourly regular dose	18	At rest	Chronic: 18 (100) Exertional: NR Other breathlessness: NR	NR	Male: 8 (44.4) Female: 10 (55.6)	Mean (SD): 61.3 (NR) Median: 65 Range: NR	NR
Allard, 1999 <sup>31</sup>	NR	Arm 2	Opioid dose 50% of 4 hourly regular dose	15	At rest	Chronic: 15 (100) Exertional: NR Other breathlessness: NR	NR	Male: 6 (40) Female: 9 (60)	Mean (SD): 65.7 (NR) Median: 67 Range: NR	NR
Bruera, 1993 <sup>32</sup>	NR	Overall	Overall	10	NR	NR	NR	NR	NR	NR
Bruera, 2005 <sup>33</sup>	KQ4	Overall	Overall	12	At rest	At rest: NR Exertional: 0 (0) Other breathlessness: 12 (100)	ECOG n (%): NR Mean (SD): NR Median: 2.5 Range: 2 to 4	Male: 4 (0.33) Female: 8 (0.66)	Mean (SD): NR Median: 58 Range: 46 to 77	NR
Charles, 2008 <sup>34</sup>	KQ4	Overall	Overall	20	Incident dyspnea	Acute: 20 (100) Exertional: NR Other breathlessness: 0 (0)	NR	Male: 11 (55) Female: 9 (45)	Mean (SD): 69 (NR) Median: NR Range: 48 to 83	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Gamborg, 2013 <sup>35</sup>	KQ4	Overall	Overall	20	NR	NR	NR	Male: 2 (10) Female: 18 (90)	Mean (SD): NR Median: NR Range: NR	NR
Gamborg, 2013 <sup>35</sup>	KQ4	Arm 1	Red Morphine Drops	9	At rest	Chronic: 9 (100) Exertional: NR Other breathlessness: NR	NR	Male: NR Female: NR	Mean (SD): NR Median: 69 Range: 42 to 79	NR
Gamborg, 2013 <sup>35</sup>	KQ4	Arm 2	Subcutaneous Morphine	11	At rest	Chronic: 11 (100) Exertional: NR Other breathlessness: NR	NR	Male: NR Female: NR	Mean (SD): NR Median: 69 Range: 50 to 84	NR
Hardy, 2016 <sup>36</sup>	KQ4	Overall	Overall	73	NR	NR	Karnofsky n (%): NR Mean (SD): NR Median: 60 Range: 30 to 80	Male: 35 (48) Female: 25 (52)	Mean (SD): NR Median: 70 Range: IQR: 62 to 78	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Hui, 2014 <sup>37</sup>	KQ4	Overall	Overall	20	Exertional	At rest: 0 (0) Exertional: 20 (100) Other breathlessness: 0 (0)	Karnofsky n (%): NR Mean (SD): 80 (8) Median: NR Range: NR	Male: 9 (45) Female: 11 (55)	Mean (SD): 55 (NR) Median: NR Range: 27 to 75	White: 14 (70) Black: 3 (15) Hispanic: 3 (15) Asian: NR Other: NR
Hui, 2014 <sup>37</sup>	KQ4	Arm 1	Placebo	10	Exertional	At rest: 0 (0) Exertional: 10 (100) Other breathlessness: 0 (0)	Karnofsky n (%): NR Mean (SD): 79 (9) Median: NR Range: NR	Male: 5 (50) Female: 5 (50)	Mean (SD): 54 (NR) Median: NR Range: 30 to 73	White: 6 (60) Black: 2 (20) Hispanic: 2 (20) Asian: NR Other: NR
Hui, 2014 <sup>37</sup>	KQ4	Arm 2	Fentanyl	10	Exertional	At rest: 0 (0) Exertional: 10 (100) Other breathlessness: 0 (0)	Karnofsky n (%): NR Mean (SD): 80 (8) Median: NR Range: NR	Male: 4 (40) Female: 6 (60)	Mean (SD): 55 (NR) Median: NR Range: 27 to 75	White: 8 (80) Black: 1 (10) Hispanic: 1 (10) Asian: NR Other: NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Hui, 2016 <sup>38</sup>	KQ4	Overall	Overall	24	Exertional	At rest: NR Exertional: 24 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 75.8 (9.7) Median: NR Range: NR	Male: 11 (45.8) Female: 13 (54.2)	Mean (SD): 52.4 (NR) Median: NR Range: 47.5 to 57.4	White: 16 (66.7) Black: 5 (20.8) Hispanic: 3 (12.5) Asian: NR Other: NR
Hui, 2016 <sup>38</sup>	KQ4	Arm 1	Placebo	12	Exertional	At rest: NR Exertional: 12 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 75.8 (10.8) Median: NR Range: NR	Male: 8 (66.6) Female: 4 (33.3)	Mean (SD): 53.3 (NR) Median: NR Range: 45 to 61.6	White: 8 (66.7) Black: 2 (16.7) Hispanic: 2 (16.7) Asian: NR Other: NR
Hui, 2016 <sup>38</sup>	KQ4	Arm 2	FPNS	12	Exertional	At rest: NR Exertional: 12 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 75.8 (9) Median: NR Range: NR	Male: 3 (25) Female: 9 (75)	Mean (SD): 51.5 (NR) Median: NR Range: 44.7 to 58.3	White: 8 (66.7) Black: 3 (25) Hispanic: 1 (8.3) Asian: NR Other: NR
Hui, 2016 <sup>39</sup>	KQ4	Overall	Overall	41	NR	NR	Karnofsky n (%): NR Mean (SD): 72 (11) Median: NR Range: NR	Male: 16 (39) Female: 25 (61)	Mean (SD): 63 (NR) Median: NR Range: 48 to 78	White: 27 (66) Black: 11 (27) Hispanic: 2 (5) Asian: 1 (2) Other: 0 (0)
Hui, 2016 <sup>39</sup>	KQ4	Arm 1	Placebo	21	NR	NR	Karnofsky n (%): NR Mean (SD): 71 (11) Median: NR Range: NR	Male: 7 (33) Female: 14 (67)	Mean (SD): 64 (NR) Median: NR Range: 48 to 78	White: 13 (62) Black: 6 (29) Hispanic: 1 (5) Asian: 1 (5) Other: 0 (0)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Hui, 2016 <sup>39</sup>	KQ4	Arm 2	Dexamethasone	20	NR	NR	Karnofsky n (%): NR Mean (SD): 74 (11) Median: NR Range: NR	Male: 9 (45) Female: 11 (55)	Mean (SD): 62 (NR) Median: NR Range: 49 to 71	White: 14 (70) Black: 5 (25) Hispanic: 1 (5) Asian: 0 (0) Other: 0 (0)
Hui, 2017 <sup>40</sup>	KQ4	Overall	All patients	20	Exertional	At rest: NR Exertional: 20 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 71 (7.9) Median: NR Range: NR	Male: 8 (40) Female: 12 (60)	Mean (SD): 55 (NR) Median: NR Range: 31 to 72	White: 13 (65) Black: 5 (25) Hispanic: 2 (10) Asian: NR Other: 0 (0)
Hui, 2017 <sup>40</sup>	KQ4	Arm 1	Placebo	11	Exertional	At rest: NR Exertional: 11 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 70 (8.9) Median: NR Range: NR	Male: 5 (45.5) Female: 6 (54.5)	Mean (SD): 57 (NR) Median: NR Range: 45 to 72	White: 6 (54.5) Black: 3 (27.3) Hispanic: 2 (18.2) Asian: NR Other: 0 (0)
Hui, 2017 <sup>40</sup>	KQ4	Arm 2	FBT	9	Exertional	At rest: NR Exertional: 9 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 72.2 (6.7) Median: NR Range: NR	Male: 3 (33.3) Female: 6 (66.7)	Mean (SD): 52 (NR) Median: NR Range: 31 to 67	White: 7 (77.8) Black: 2 (22.2) Hispanic: 0 (0) Asian: NR Other: 0 (0)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Hui, 2019 <sup>41</sup>	KQ4	Overall	Overall	30	Exertional	At rest: NR Exertional: 30 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 72 (9.6) Median: NR Range: NR	Male: 10 (33.3) Female: 20 (66.7)	Mean (SD): 52 (13) Median: NR Range: NR	White: 23 (76.7) Black: 1 (3.3) Hispanic: 5 (16.7) Asian: 1 (3.3) Other: NR
Hui, 2019 <sup>41</sup>	KQ4	Arm 1	High dose fentanyl	13	Exertional	At rest: NR Exertional: 13 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 73.9 (10.4) Median: NR Range: NR	Male: 4 (30.8) Female: 9 (69.2)	Mean (SD): 53 (16) Median: NR Range: NR	White: 11 (84.6) Black: 0 (0) Hispanic: 2 (15.4) Asian: 0 (0) Other: NR
Hui, 2019 <sup>41</sup>	KQ4	Arm 2	Low dose fentanyl	17	Exertional	At rest: NR Exertional: 17 (100) Other breathlessness: NR	Karnofsky n (%): NR Mean (SD): 70.6 (9) Median: NR Range: NR	Male: 6 (35.3) Female: 11 (64.7)	Mean (SD): 51 (10) Median: NR Range: NR	White: 12 (70.6) Black: 1 (5.9) Hispanic: 3 (17.6) Asian: 1 (5.9) Other: NR
Kawabata, 2013 <sup>42</sup>	KQ4	Overall	Overall	95	NR	NR	ECOG n (%): PS 0: 0, PS 1: 2, PS 2: 9, PS 3: 36, PS 4: 49 (Episodes) (NR) Mean (SD): NR Median: NR Range: NR	Male: 53 (55.8) Female: 42 (44.2)	Mean (SD): 71.7 (NR) Median: NR Range: 47 to 92	NR
Navigante, 2006 <sup>43</sup>	KQ4	Arm 1	Morphine	35	At rest	At rest: 35 (100) Exertional: NR Other breathlessness: NR	NR	Male: 18 (51.4) Female: 17 (48.6)	Mean (SD): 57.3 (NR) Median: NR Range: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Navigante, 2006 <sup>43</sup>	KQ4	Arm 2	Midazolam	33	At rest	At rest: 33 (100) Exertional: NR Other breathlessness: NR	NR	Male: 13 (39.4) Female: 20 (60.6)	Mean (SD): 57.8 (NR) Median: NR Range: NR	NR
Navigante, 2006 <sup>43</sup>	KQ4	Arm 3	Morphine+Midazolam	33	At rest	At rest: 33 (100) Exertional: NR Other breathlessness: NR	NR	Male: 16 (48.5) Female: 17 (51.5)	Mean (SD): 56.9 (NR) Median: NR Range: NR	NR
Navigante, 2010 <sup>44</sup>	KQ4	Arm 1	Morphine	31	At rest	At rest: 31 (100) Exertional: 0 (0) Other breathlessness: 0 (0)	ECOG n (%): NR Mean (SD): NR (median absolute deviation: 0) Median: 2 Range: NR	Male: NR Female: NR	Mean (SD): NR Median: 55 Range: 30 to 80	NR
Navigante, 2010 <sup>44</sup>	KQ4	Arm 2	Midazolam	32	At rest	At rest: 32 (100) Exertional: 0 (0) Other breathlessness: 0 (0)	ECOG n (%): NR Mean (SD): NR (median absolute deviation: 0) Median: 2 Range: NR	Male: NR Female: NR	Mean (SD): NR Median: 59 Range: 36 to 82	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Peoples, 2016 <sup>45</sup>	NR	Arm 1	Placebo	192	Exertional	At rest: NR Exertional: 192 (100) Other breathlessness: NR	NR	Male: 97 (50.5) Female: 95 (49.5)	Mean (SD): 64 (9.4) Median: NR Range: NR	White: 171 (89.1) Black: 20 (10.4) Hispanic: 2 (1) Asian: NR Other: 1 (0.5)
Peoples, 2016 <sup>45</sup>	NR	Arm 2	Buspirone	187	Exertional	At rest: NR Exertional: 187 (100) Other breathlessness: NR	NR	Male: 87 (46.5) Female: 100 (53.5)	Mean (SD): 62.9 (10.3) Median: NR Range: NR	White: 166 (88.8) Black: 19 (10.2) Hispanic: 0 (0) Asian: NR Other: 2 (1)
Pinna, 2015 <sup>46</sup>	KQ4	Overall	Overall	13	Exertional	At rest: 0 (0) Exertional: 13 (100) Other breathlessness: 0 (0)	Karnofsky n (%): 13 (100) Mean (SD): NR Median: NR Range: NR	Male: 11 (84.6) Female: 2 (15.4)	Mean (SD): 65.2 (10.4) Median: NR Range: NR	NR
Simon, 2016 <sup>47</sup>	NR	Overall	Overall	10	Episodic	Acute: 10 (100) Exertional: NR Other breathlessness: 0 (0)	Karnofsky n (%): NR Mean (SD): 67 (10.6) Median: NR Range: NR	Male: 6 (60) Female: 4 (40)	Mean (SD): 58 (11.3) Median: NR Range: NR	NR
Tian, 2016 <sup>48</sup>	KQ4	Arm 1	Morphine	118	NR	NR	NR	Male: 61 (51.7) Female: 57 (48.3)	Mean (SD): 54.2 (NR) Median: NR Range: NR	NR
Tian, 2016 <sup>48</sup>	KQ4	Arm 2	Methylprednisolone	111	NR	NR	NR	Male: 54 (48.6) Female: 58 (52.3)	Mean (SD): 53.1 (NR) Median: NR Range: NR	NR
Tian, 2016 <sup>48</sup>	KQ4	Arm 3	Aminophylline	114	NR	NR	NR	Male: 60 (52.6) Female: 54 (47.4)	Mean (SD): 53.7 (NR) Median: NR Range: NR	NR

ECOG= Eastern Cooperative Oncology Group Performance Status; FPNS= fentanyl pectin nasal spray; IQR=interquartile range; KQ4=Key Question 4; n=population; NR=not reported; SD=standard deviation



**Evidence Table D-10. Participant cancer and comorbidity characteristics for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Aabom, 2019 <sup>30</sup>	NR	Overall	Overall	12	Lung and non-lung	Lung/Mesothelioma: 8 (66.67) Non-lung/mesothelioma: 4 (33.33)	Advanced: 12 (100)	NR	Opioids: 7 (58.33)	COPD: 4 (33.33) Heart failure: NR Asthma: NR Heart disease: 2 (16.67)
Allard, 1999 <sup>31</sup>	NR	Overall	Overall	33	Breast, Lung/Pleura, Other (not specified)	Lung/Mesothelioma: 21 (63.6) Non-lung/mesothelioma: 12 (36.4)	NR	NR	Nebulized medications (not specified): 16 (48.5)	NR
Allard, 1999 <sup>31</sup>	NR	Arm 1	Opioid dose 25% of 4 hourly regular dose	18	Breast, Lung/Pleura, Other (not specified)	Lung/Mesothelioma: 12 (66.7) Non-lung/mesothelioma: 6 (33.3)	NR	NR	Nebulized medications (not specified): 8 (44.4)	NR
Allard, 1999 <sup>31</sup>	NR	Arm 2	Opioid dose 50% of 4 hourly regular dose	15	Breast, Lung/Pleura, Other (not specified)	Lung/Mesothelioma: 9 (60) Non-lung/mesothelioma: 6 (40)	NR	NR	Nebulized medications (not specified): 8 (53.3)	NR
Bruera, 1993 <sup>32</sup>	NR	Overall	Overall	10	Lung (others not specified)	NR	Terminal: 10 (100)	NR	Opioids: 10 (100)	NR
Bruera, 2005 <sup>33</sup>	KQ4	Overall	Overall	12	Lung, Gastrointestinal, Other	Lung/Mesothelioma: 7 (58) Non-lung/mesothelioma: 5 (42)	Metastatic: NR	NR	NR	NR
Charles, 2008 <sup>34</sup>	KQ4	Overall	Overall	20	Breast, Lung, Mesothelioma, Prostate, Renal	Lung/Mesothelioma: 15 (75) Non-lung/mesothelioma: 5 (25)	NR	NR	Nebulized medications (not narcotics): 8 (40), Continuous oxygen: 13 (65)	NR
Gamborg, 2013 <sup>35</sup>	KQ4	Overall	Overall	20	NR	Lung/Mesothelioma: NR Non-lung/mesothelioma: NR	NR	NR	NR	NR
Gamborg, 2013 <sup>35</sup>	KQ4	Arm 1	Red Morphine Drops	9	Lung	Lung/Mesothelioma: 9 (100) Non-lung/mesothelioma: 0 (0)	Advanced primary: NR, Metastatic: NR	NR	Steroids: NR, Nasal oxygen: 4 (44.4)	NR
Gamborg, 2013 <sup>35</sup>	KQ4	Arm 2	Subcutaneous Morphine	11	Lung	Lung/Mesothelioma: 11 (100) Non-lung/mesothelioma: 0 (0)	Advanced primary: NR, Metastatic: NR	NR	Steroids: NR, Nasal oxygen: 4 (36.4)	NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Hardy, 2016 <sup>36</sup>	KQ4	Overall	Overall	73	Cancer (not specified)	Lung/Mesothelioma: NR Non-lung/mesothelioma: NR	Cancer in palliative care (not specified): 50 (67)	NR	NR	NR
Hui, 2014 <sup>37</sup>	KQ4	Overall	Overall	20	Breast, Gastrointestinal, Genitourinary, Gynecologic, Lung, Sarcoma	Lung/Mesothelioma: 4 (20) Non-lung/mesothelioma: NR	Stage III: 4 (20), Stage IV: 13 (65)	NR	Opioids: 20 (100), Bronchodilators: 1 (5), Steroids: 1 (5), Standard supplemental oxygen: 1 (5)	COPD: 1 (5) Heart failure: 0 (0) Asthma: 3 (15) Bronchiectasis: 0 (0)
Hui, 2014 <sup>37</sup>	KQ4	Arm 1	Placebo	10	Breast, Gastrointestinal, Genitourinary, Gynecologic, Lung, Sarcoma	Lung/Mesothelioma: 3 (30) Non-lung/mesothelioma: NR	Stage III: 3 (30), Stage IV: 6 (60)	NR	Opioids: 10 (100), Bronchodilators: 1 (10), Steroids: 1 (10), Standard supplemental oxygen: 0 (0)	COPD: 0 (0) Heart failure: 0 (0) Asthma: 1 (10) Bronchiectasis: 0 (0)
Hui, 2014 <sup>37</sup>	KQ4	Arm 2	Fentanyl	10	Breast, Gastrointestinal, Genitourinary, Gynecologic, Lung, Sarcoma	Lung/Mesothelioma: 1 (10) Non-lung/mesothelioma: NR	Stage III: 1 (10), Stage IV: 7 (70)	NR	Opioids: 10 (100), Bronchodilators: 0 (0), Steroids: 0 (0), Standard supplemental oxygen: 1 (10)	COPD: 1 (10) Heart failure: 0 (0) Asthma: 2 (20) Bronchiectasis: 0 (0)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Hui, 2016 <sup>38</sup>	KQ4	Overall	Overall	24	Breast, Gastrointestinal, Genitourinary, Gynecologic, Lung, Hematologic, Other	Lung/Mesothelioma: 3 (12.5) Non-lung/mesothelioma: 21 (87.5)	Localized/Localized advanced: 6 (25), Metastatic/refractory: 18 (75)	NR	Opioids: 24 (100), Bronchodilators: 11 (45.8), Standard supplemental oxygen: 2 (8.3)	COPD: 4 (16.7) Heart failure: 1 (4.2) Asthma: 5 (20.8) Bronchiectasis: 0 (0)
Hui, 2016 <sup>38</sup>	KQ4	Arm 1	Placebo	12	Breast, Gastrointestinal, Genitourinary, Gynecologic, Lung, Hematologic, Other	Lung/Mesothelioma: 2 (16.7) Non-lung/mesothelioma: 10 (83.3)	Localized/Localized advanced: 2 (16.6), Metastatic/refractory: 10 (83.4)	NR	Opioids: 12 (100), Bronchodilators: 5 (41.7), Standard supplemental oxygen: 1 (8.3)	COPD: 2 (16.7) Heart failure: 0 (0) Asthma: 0 (0) Bronchiectasis: 0 (0)
Hui, 2016 <sup>38</sup>	KQ4	Arm 2	FPNS	12	Breast, Gastrointestinal, Genitourinary, Gynecologic, Lung, Hematologic, Other	Lung/Mesothelioma: 1 (8.3) Non-lung/mesothelioma: 11 (91.7)	Localized/Localized advanced: 4 (33.3), Metastatic/refractory: 8 (66.7)	NR	Opioids: 12 (100), Bronchodilators: 6 (50), Standard supplemental oxygen: 1 (8.3)	COPD: 2 (16.7) Heart failure: 1 (8.3) Asthma: 5 (41.7) Bronchiectasis: 0 (0)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Hui, 2016 <sup>39</sup>	KQ4	Overall	Overall	41	NSCLC, small cell lung cancer, Mesothelioma, other	Lung/Mesothelioma: 37 (90) Non-lung/mesothelioma: 4 (10)	Localized: 5 (12), Locally advanced: 7 (17), Metastatic/re current: 29 (71)	NR	Regular opioids: 15 (37), As needed opioids: 20 (49), Regular Bronchodilators: 4 (10), As needed Bronchodilators: 8 (20), Regular Supplemental oxygen: 3 (7), As needed Standard supplemental oxygen: 1 (2)	COPD: 9 (22) Heart failure: NR Asthma: 3 (7)
Hui, 2016 <sup>39</sup>	KQ4	Arm 1	Placebo	21	NSCLC, small cell lung cancer, Mesothelioma, other	Lung/Mesothelioma: 20 (95) Non-lung/mesothelioma: 1 (5)	Localized: 1 (5), Locally advanced: 4 (19), Metastatic/re current: 16 (76)	NR	Regular opioids: 9 (43), As needed opioids: 11 (52), Regular Bronchodilators: 3 (14), As needed Bronchodilators: 4 (19), Regular Supplemental oxygen: 3 (14), As needed Standard supplemental oxygen: 1 (5)	COPD: 7 (33) Heart failure: NR Asthma: 2 (10)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Hui, 2016 <sup>39</sup>	KQ4	Arm 2	Dexamethasone	20	NSCLC, small cell lung cancer, Mesothelioma, other	Lung/Mesothelioma: 17 (85) Non-lung/mesothelioma: 3 (15)	Localized: 4 (20), Locally advanced: 3 (15), Metastatic/recurrent: 13 (65)	NR	Regular opioids: 6 (30), As needed opioids: 9 (45), Regular Bronchodilators: 1 (5), As needed Bronchodilators: 4 (20), Regular Standard supplemental oxygen: 0 (0), As needed Supplemental oxygen: 0 (0)	COPD: 2 (10) Heart failure: NR Asthma: 1 (5)
Hui, 2017 <sup>40</sup>	KQ4	Overall	All patients	20	Breast, GI, GU, Gyn, Lung, Other	Lung/Mesothelioma: 8 (40) Non-lung/mesothelioma: 12 (60)	Metastatic: 18 (90), Locally advanced: 1 (5)	NR	Opioids: 20 (100), Bronchodilators: 2 (10), Steroids: 4 (20), Standard supplemental oxygen: 0 (0)	COPD: 3 (15) Heart failure: 1 (5) Asthma: 1 (5) Bronchiectasis: 0 (0)
Hui, 2017 <sup>40</sup>	KQ4	Arm 1	Placebo	11	Breast, GI, GU, Gyn, Lung, Other	Lung/Mesothelioma: 5 (45.5) Non-lung/mesothelioma: 6 (54.5)	Metastatic 10 (91), Locally advanced: 1 (9.1)	NR	Opioids: 11 (100), Bronchodilators: 1 (9.1), Steroids: 1 (9.1), Standard supplemental oxygen: 0 (0)	COPD: 1 (9.1) Heart failure: 1 (9.1) Asthma: 0 (0) Bronchiectasis: 0 (0)
Hui, 2017 <sup>40</sup>	KQ4	Arm 2	FBT	9	Breast, GI, GU, Lung, Other	Lung/Mesothelioma: 3 (33.3) Non-lung/mesothelioma: 6 (66.6)	Metastatic/recurrent : 9 (100)	NR	Opioids: 9 (100), Bronchodilators: 1 (11.1), Steroids: 3 (33.3), Standard supplemental oxygen: 0 (0)	COPD: 2 (22.2) Heart failure: 0 (0) Asthma: 1 (11.1) Bronchiectasis: 0 (0)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Hui, 2019 <sup>41</sup>	KQ4	Overall	Overall	30	Breast, Gastrointestinal, Genitourinary, Gynecological, Head and neck, Respiratory, Other (not specified)	Lung/Mesothelioma: 7 (23.3) Non-lung/mesothelioma: 23 (76.7)	Metastatic: 24 (80), Locally advanced: 5 (16.7), Localized: 1 (3.3)	NR	Scheduled concurrent: Opioids: 30 (100), Bronchodilators: 2 (6.7), Steroids: 4 (13.3), Standard supplemental oxygen: 1 (*3.3)	COPD: 4 (13.3) Heart failure: NR Asthma: NR
Hui, 2019 <sup>41</sup>	KQ4	Arm 1	High dose fentanyl	13	Breast, Gastrointestinal, Genitourinary, Gynecological, Head and neck, Respiratory, Other (not specified)	Lung/Mesothelioma: 4 (30.8) Non-lung/mesothelioma: 9 (69.2)	Metastatic: 10 (76.9), Locally advanced: 3 (23.1), Localized: 0 (0)	NR	Scheduled concurrent: Opioids: 13 (100), Bronchodilators: 1 (7.7), Steroids: 1 (7.7), Standard supplemental oxygen: 1 (7.7)	COPD: 1 (7.7) Heart failure: NR Asthma: NR
Hui, 2019 <sup>41</sup>	KQ4	Arm 2	Low dose fentanyl	17	Breast, Gastrointestinal, Genitourinary, Gynecological, Head and neck, Respiratory, Other (not specified)	Lung/Mesothelioma: 3 (17.6) Non-lung/mesothelioma: 14 (82.4)	Metastatic: 14 (82.4), Locally advanced: 2 (11.8), Localized: 1 (5.9)	NR	Scheduled concurrent: Opioids: 17 (100), Bronchodilators: 1 (5.9), Steroids: 3 (17.6), Standard supplemental oxygen: 0 (0)	COPD: 3 (17.6) Heart failure: NR Asthma: NR



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Kawabata, 2013 <sup>42</sup>	KQ4	Overall	Overall	95	Adipose tissue , Colon , Esophagus , Gall bladder , Head and neck , Kidney , Liver , Lung , Lymph node , Mammary gland , Mesothelium , Multiple origins , Ovary , Pancreas , Peritoneum , Prostate , Skin , Stomach , Unknown, Urinary tract , Uterus	Lung/Mesothelioma: 24 (25.3) Non-lung/mesothelioma: 71 (74.7)	NR	NR	Nonsteroidal anti-inflammatory drugs: 44 episodes (45.8), Analgesic adjuvants: 7 episodes (7.32), Oxygen: 39 episodes (40.6)	NR
Navigante, 2006 <sup>43</sup>	KQ4	Arm 1	Morphine	35	Lung, Breast, Gynecologic, Sarcomas, Unknown primary, Colorectal, Other	Lung/Mesothelioma: 12 (34.3) Non-lung/mesothelioma: 23 (65.7)	Terminal advanced cancer: 35 (100)	NR	NR	COPD: NR Heart failure: NR Asthma: NR Any kind of airway/lung affection: 32 (91.4)
Navigante, 2006 <sup>43</sup>	KQ4	Arm 2	Midazolam	33	Lung, Breast, Gynecologic, Sarcomas, Unknown primary, Colorectal, Other	Lung/Mesothelioma: 8 (24.3) Non-lung/mesothelioma: 25 (75.7)	Terminal advanced cancer: 33 (100)	NR	NR	COPD: NR Heart failure: NR Asthma: NR Any kind of airway/lung affection: 29 (88)
Navigante, 2006 <sup>43</sup>	KQ4	Arm 3	Morphine+Midazolam	33	Lung, Breast, Gynecologic, Sarcomas, Unknown primary, Colorectal, Other	Lung/Mesothelioma: 10 (30.3) Non-lung/mesothelioma: 23 (69.7)	Terminal advanced cancer: 33 (100)	NR	NR	COPD: NR Heart failure: NR Asthma: NR Any kind of airway/lung affection: 31 (94)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Navigante, 2010 <sup>44</sup>	KQ4	Arm 1	Morphine	31	Breast, Head and neck, Lung, Other	Lung/Mesothelioma: 8 (25.8) Non-lung/mesothelioma: 23 (74.2)	NR	NR	NR	NR
Navigante, 2010 <sup>44</sup>	KQ4	Arm 2	Midazolam	32	Breast, Head and neck, Lung, Other	Lung/Mesothelioma: 8 (25) Non-lung/mesothelioma: 24 (75)	NR	NR	NR	NR
Peoples, 2016 <sup>45</sup>	NR	Arm 1	Placebo	192	Lung, Breast, Gastrointestinal, Other	Lung/Mesothelioma: 118 (61.5) Non-lung/mesothelioma: 74 (38.5)	Stage 1: 12 (6.3), Stage 2: 18 (9.4), Stage 3: 53 (27.6), Stage 4: 102 (53.1)	Systemic, Chemotherapy alone: 192 (100)NR	NR	COPD: 69 (35.9) Heart failure: NR Asthma: NR
Peoples, 2016 <sup>45</sup>	NR	Arm 2	Buspirone	187	Lung, Breast, Gastrointestinal, Other	Lung/Mesothelioma: 114 (61) Non-lung/mesothelioma: 73 (39)	Stage 1: 10 (5.3), Stage 2: 17 (9.1), Stage 3: 49 (26.2), Stage 4: 103 (55.1)	Systemic, Chemotherapy alone: 187 (100)NR	NR	COPD: 28 (36.4) Heart failure: NR Asthma: NR
Pinna, 2015 <sup>46</sup>	KQ4	Overall	Overall	13	Breast, Kidney, Lung, Stomach	Lung/Mesothelioma: 10 (76.9) Non-lung/mesothelioma: 3 (23.1)	Advanced cancer: 13 (100)	NR	NR	NR
Simon, 2016 <sup>47</sup>	NR	Overall	Overall	10	Lung, Hematology, Breast, Ovary, Esophagus, Melanoma	Lung/Mesothelioma: 4 (40) Non-lung/mesothelioma: 6 (60)	Incurable: 10 (100)	NR	NR	Charlson Comorbidity Index (CCI) Mean: 6.8 (SD 2.9)



Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Tian, 2016 <sup>48</sup>	KQ4	Arm 1	Morphine	118	Breast, Colorectal, Gastric, Lung, Other (not specified)	Lung/Mesothelioma: 45 (38.1) Non-lung/mesothelioma: 73 (61.9)	Advanced, not specified: 118 (100)	NR	NR	NR
Tian, 2016 <sup>48</sup>	KQ4	Arm 2	Methylprednisolone	111	Breast, Colorectal, Gastric, Lung, Other (not specified)	Lung/Mesothelioma: 37 (33.3) Non-lung/mesothelioma: 74 (66.7)	Advanced, not specified: 111 (100)	NR	NR	NR
Tian, 2016 <sup>48</sup>	KQ4	Arm 3	Aminophylline	114	Breast, Colorectal, Gastric, Lung, Other (not specified)	Lung/Mesothelioma: 43 (37.7) Non-lung/mesothelioma: 71 (62.3)	Advanced, not specified: 114 (100)	NR	NR	NR

COPD= Chronic obstructive pulmonary disease; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; GI=gastrointestinal; GU= genitourinary tract; KQ4=Key Question 4; n=population; NR=not reported; NSCLC=non-small cell lung cancer



**Evidence Table D-11. Participant demographic characteristics for studies comparing combination non-pharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Type of Breathlessness Being Treated	Breathlessness, n (%)	Performance Status	Sex	Age	Race, n (%)
Gottlieb, 2020 <sup>49</sup>	NR	Arm 1	Control	57	NR	NR	Not specified 0= 25 (44), 1 = 25 (44), 2= 7 (12)	Male: 39 (67.4) Female: 18 (31.6)	Mean (SD): 67.2 (8.1)	NR
Gottlieb, 2020 <sup>49</sup>	NR	Arm 2	Intervention	57	NR	NR	Not specified 0= 25 (44), 1= 26 (46), 6 (10)	Male: 33 (57.9) Female: 24 (42.1)	Mean (SD): 67.6 (8.3)	NR
Minchom, 2016 <sup>50</sup>	KQ4	Arm 1	Acupuncture	57	NR	At rest: NR Exertional: NR Other breathlessness: 57 (100)	ECOG n (%): 0/1: 27, 2: 23, 3: 7 (NR) Mean (SD): NR Median: NR Range: NR	Male: 40 (70.2) Female: 17 (29.8)	Mean (SD): NR Median: 74 Range: 50 to 88	NR
Minchom, 2016 <sup>50</sup>	KQ4	Arm 2	Morphine	60	NR	At rest: NR Exertional: NR Other breathlessness: 60 (100)	ECOG n (%): 0/1: 30, 2: 22, 3: 8 (NR) Mean (SD): NR Median: NR Range: NR	Male: 36 (60) Female: 24 (40)	Mean (SD): NR Median: 75 Range: 42 to 87	NR
Minchom, 2016 <sup>50</sup>	KQ4	Arm 3	Acupuncture+Morphine	56	NR	At rest: NR Exertional: NR Other breathlessness: 56 (100)	ECOG n (%): 0/1: 24, 2: 24, 3: 8 (NR) Mean (SD): NR Median: NR Range: NR	Male: 38 (67.9) Female: 18 (32.1)	Mean (SD): NR Median: 70 Range: 49 to 88	NR

ECOG= Eastern Cooperative Oncology Group Performance Status; KQ4=Key Question 4; n= population; NR=not reported; SD=standard deviation



**Evidence Table D-12. Participant cancer and comorbidity characteristics for studies comparing combination non-pharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Arm	Arm Name	Number at Baseline	Cancer Types	Cancer Types, n (%)	Cancer Stage, n (%)	Cancer Treatment, n (%)	Concurrent Therapies, n (%)	Comorbidities, n (%)
Gottlieb, 2020 <sup>49</sup>	NR	Arm 1	Control	57	Lung, head and neck	Lung/Mesothelioma: 47 (83) Non-lung/mesothelioma: 10 (17)	III, IV: 49 (86%)	NR	NR	COPD: 57 (100) Heart failure: 6 (11) Asthma: 0 (0) Diabetes mellitus: 5 (9)
Gottlieb, 2020 <sup>49</sup>	NR	Arm 2	Intervention	57	Lung, head and neck	Lung/Mesothelioma: 48 (84) Non-lung/mesothelioma: 9 (16)	III, IV: 47 (82%)	NR	NR	COPD: 57 (100) Heart failure: 7 (12) Asthma: 0 (0) Diabetes mellitus: 8 (14)
Minchom, 2016 <sup>50</sup>	KQ4	Arm 1	Acupuncture	57	NSCLC, Mesothelioma	Lung/Mesothelioma: 57 (100) Non-lung/mesothelioma: 0 (0)	NR	NR	NR	NR
Minchom, 2016 <sup>50</sup>	KQ4	Arm 2	Morphine	60	NSCLC, Mesothelioma	Lung/Mesothelioma: 60 (100) Non-lung/mesothelioma: 0 (0)	NR	NR	NR	NR
Minchom, 2016 <sup>50</sup>	KQ4	Arm 3	Acupuncture+Morphine	56	NSCLC, Mesothelioma	Lung/Mesothelioma: 56 (100) Non-lung/mesothelioma: 0 (0)	NR	NR	NR	NR

III=Cancer stage 3; IV=Cancer stage 4; KQ4=Key Question 4; n= population; NR=not reported



**Evidence Table D-13. Intervention characteristics for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Booth, 1996 <sup>1</sup>	NR	Arm 1	Air first	Yes	Room air by nasal cannula  Mode of administration: In-person  Dose 4 Litre/ minute  Frequency: Once Duration: 15 minutes Administered: NR	NR	NR	NR	NR	NR
Booth, 1996 <sup>1</sup>	NR	Arm 2	Standard supplemental oxygen first	Yes	Oxygen by nasal cannula  Mode of administration: In-person  Dose 4 Litre/ minute  Frequency: Once Duration: 15 minutes Administered: NR	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, N (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Bordeleau, 2003 <sup>2</sup>	KQ4	Arm 1	Control	Yes	Usual information regarding breast cancer, treatment, relaxation, nutrition  Mode of administration: In-person  Dose  Frequency: Duration: Administered by	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Bordeleau, 2003 <sup>2</sup>	KQ4	Arm 2	Intervention	Yes	<p>Therapist-led support group: supportive-expressive therapy, foster support and encourage emotions expressing, relaxation exercise at end of session, encouraged to practice at home</p> <p>Mode of administration: In-person</p> <p>Dose Groups of 6-10 participants and 2 leaders</p> <p>Frequency: Weekly Duration: 90 minutes Administered by Psychiatrists, psychologists, social workers, or nurse clinicians (trained in a 2-day workshop, monthly videotape review, refresher workshop every 9-12 months)</p>	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Bruera, 1993 <sup>3</sup>	NR	Arm 1	Air first	Yes	Room air by face mask  Mode of administration: In-person  Dose 5 Litre/ minute  Frequency: Once Duration: 5 minutes Administered: NR	NR	NR	NR	NR	NR
Bruera, 1993 <sup>3</sup>	NR	Arm 2	Oxygen first	Yes	Oxygen by face mask  Mode of administration: In-person  Dose 5 Litre/ minute  Frequency: Once Duration: 5 minutes Administered: NR	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Bruera, 2003 <sup>4</sup>	KQ4	Arm 1	Air	Yes	Room air by nasal cannula  Mode of administration: In-person  Dose 5 Litre/ minute  Frequency: Once throughout intervention (5 min rest and then 6 minute walk) Duration: 11 minutes Administered by Respiratory therapists	NR	NR	NR	NR	NR
Bruera, 2003 <sup>4</sup>	KQ4	Arm 2	Standard Supplemental oxygen	Yes	Oxygen by nasal cannula  Mode of administration: In-person  Dose 5 Litre/ minute  Frequency: Once throughout intervention (5 min rest and then 6 minute walk) Duration: 11 minutes Administered by Respiratory therapists	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Chan, 2011 <sup>5</sup>	KQ4	Arm 1	Control	Yes	Usual care- pre- radiation education  Mode of administration: In-person  Dose  Frequency: Twice, baseline and at 3 weeks Duration: 40-minute each Administered by Trained nurses and social worker	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Chan, 2011 <sup>5</sup>	KQ4	Arm 2	Psychoeducational intervention (PEI)	Yes	<p>Education package (leaflet/ audiotape) and coaching on progressive muscle relaxation and self-care; cool air, means of dealing with frightening thoughts during respiratory distress, ask to practice at home daily and record in a diary</p> <p>Mode of administration: Combination In person and at home</p> <p>Dose 40-minute session</p> <p>Frequency: Twice, baseline and at 3 weeks Duration: 40-minute each Administered by Trained nurses and social worker (2 day training session, at least 2 years clinical experience)</p>	<p>New breathing technique (slow deep breaths through pursed lips), positioning, relaxation exercise</p> <p>Mode of administration:</p>	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Corner, 1996 <sup>6</sup>	KQ4	Arm 1	Control	Yes	<p>Allowed to talk freely about dyspnea but no specific counseling/ retraining given</p> <p>Mode of administration: In-person</p> <p>Dose</p> <p>Frequency: Duration: Administered by</p>	NR	NR	NR	NR	NR
Corner, 1996 <sup>6</sup>	KQ4	Arm 2	Nurse led intervention	Yes	<p>Breathing re-training, involve caregivers, held weekly, new targets/ goals set</p> <p>Mode of administration: In-person</p> <p>Dose For 3-6 weeks, more as needed</p> <p>Frequency: Weekly Duration: 1 hour Administered by Trained nurse</p>	<p>Counseling, relaxation, coping, adaptation strategies discussed</p> <p>Mode of administration: In-person</p> <p>Dose For 3-6 weeks, more as needed</p> <p>Frequency: Weekly Duration: 1 hour Administered by Trained nurse</p>	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Dhillon, 2017 <sup>7</sup>	KQ4	Arm 1	Usual care	NR	Usual care plus cancer-specific exercise (Move Your Body) and nutrition (Eat For Health) education materials  Dose NR  Frequency: NR Duration: NR Administered by NR	NR	NR	NR	NR	NR
Dhillon, 2017 <sup>7</sup>	KQ4	Arm 2	Exercise	NR	Exercise with trainer  Dose Goal was to increase recreational activity by >3 MET h/week. Home exercise encouraged. Received pedometer, activity diary, and workbook.  Frequency: 8x weekly sessions Duration: 1 hour sessions (45 minutes activity, 15 minutes behavioral support) Administered by Exercise trainer	Behavior change program based on Theory of Planned Behavior  Dose Discuss goal setting/ planning, social support, stimulus control and decision balance, physical activity and pedometer education.  Frequency: 8x weekly sessions Duration: 1 hour sessions (45 minutes activity, 15 minutes behavioral support) Administered by Exercise trainer	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Dogan, 2019 <sup>8</sup>	KQ4	Arm 1	Control	NR	Standard care  Mode of administration: In-person  NR	NR	NR	NR	NR	NR
Dogan, 2019 <sup>8</sup>	KQ4	Arm 2	Acupressure	NR	Acupressure  Mode of administration: In person, telephone, and at home  Dose First session carried out by investigator. Participants/ caregivers instructed by investigator on correct site/ technique. Three selected sites (LU-1, LU-10, P-6) marked by surgical pen. A training guide/ tool given to patients and primary care providers. Weekly check ins by phone.  Frequency: Twice daily Duration: 3 minutes per site (6 sites), 18 minutes per session, 36 minutes per day Administered by Trained member of the research team. No other details given.	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Farquhar, 2014 <sup>9</sup>	KQ4	Arm 1	Control	Yes	Standard including palliative care  Mode of administration: In-person  Dose  Frequency: Duration: Administered by	NR	NR		NR	NR
Farquhar, 2014 <sup>9</sup>	KQ4	Arm 2	Intervention	Yes	Being evaluated in BIS (breathlessness intervention service)  Mode of administration: Combination In person and over phone  Dose Exercise plan, airway clearance, activity pacing  Frequency: 1-4 visits to home by 1-2 concerned specialists lasting 1-1.5 hours each, 4-6 telephone calls within 2 weeks Duration: Administered by Multidisciplinary team: palliative care, occupational therapist, physical therapist	Support, caregiver support, education, anxiety control, lifestyle adjustment, reassurance, education, nutrition and sleep guidance  Mode of administration:	Mindfulness CD  Mode of administration: NR  NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Henke, 2014 <sup>10</sup>	KQ4	Arm 1	Control	Yes	Conventional physiotherapy, including massage therapy if needed  Mode of administration: In-person  Dose  Frequency: As needed Duration: Administered by Trained physiotherapist	Breathing techniques taught  Mode of administration: In-person  Dose NR  Frequency: As needed Duration: NR Administered: NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Henke, 2014 <sup>10</sup>	KQ4	Arm 2	Intervention	Yes	<p>Strength training (4 groups- trunk arm , leg, abdomen, with elastic bands, every other day), endurance training (6 min hallway walk, 2 min stairs, 5 days a week) from start to chemo cycle 1 to end of chemo cycle 3</p> <p>Mode of administration: In-person</p> <p>Dose Goal HR during endurance was 55-70% of heart rate reserve (modified depending on dyspnea score), goal repetitions during strength were 50% of maximal capacity</p> <p>Frequency: Every other day for strength, 5 days a week for endurance Duration: Administered by Trained physiotherapist</p>	<p>Physiotherapeutic breathing techniques such as active cycle of breathing (ACBT)</p> <p>Mode of administration: In-person</p> <p>Dose</p> <p>Frequency: 5 days a week Duration: Administered by Trained physiotherapist</p>	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Hui, 2013 <sup>11</sup>	KQ4	Arm 1	Bilevel positive airway pressure (BiPAP)	Yes	Bipap  Mode of administration: In-person  Dose Target inspiratory pressure 8-18 / target expiratory pressure 3-10 (cm of H2O)  Frequency: Once Duration: 2 hours Administered by Respiratory therapists	NR	NR		NR	NR
Hui, 2013 <sup>11</sup>	KQ4	Arm 2	High flow oxygen (HFO)	Yes	High flow oxygen  Mode of administration: In-person  Dose Oxygen flow, 10- 40, titrated to comfort (Litre/ minute)  Frequency: Once Duration: 2 hours Administered by Respiratory therapists	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Hwang, 2012 <sup>12</sup>	NR	Arm 1	Control	Yes	<p>General education, social phone calls, elastic band exercise given if patients asked.</p> <p>Mode of administration: In-person</p> <p>Dose</p> <p>Frequency: Duration: Administered by</p>	NR	NR		NR	NR
Hwang, 2012 <sup>12</sup>	NR	Arm 2	Exercise	Yes	<p>Treadmill/ cycling ergometer</p> <p>Mode of administration: In-person</p> <p>Dose 30-40 minute session Alternating (2-3 minutes) High intensity (80% Vo2 peak), moderate intensity (60% Vo2 peak), 10 minute warm-up, 5 minute cool down under 1:1 supervision, adjusted 1-2 weekly</p> <p>Frequency: Thrice a week x 8 weeks= 24 sessions Duration: Administered by Trained physiotherapist</p>	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Kako, 2018 <sup>13</sup>	NR	Arm 1	Fan to legs (control)	Yes	<p>Fan to legs</p> <p>Mode of administration: In-person</p> <p>Dose Fan to exposed legs</p> <p>Frequency: Once Duration: 5 minutes Administered by Investigator</p>	NR	NR		NR	NR
Kako, 2018 <sup>13</sup>	NR	Arm 2	Fan to face	Yes	<p>Fan to face</p> <p>Mode of administration: In-person</p> <p>Dose Standing fan to one side of exposed face (region of 2nd/3rd portion of trigeminal nerve), slowest speed to start, distance/ location/ side of face/ strength/ swing per patient preference</p> <p>Frequency: Once Duration: 5 minutes Administered by Investigator</p>	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Ligibel, 2016 <sup>14</sup>	NR	Arm 1	Control	Yes	Usual care (routine care)  Dose NR  Frequency: NR Duration: NR Administered by NR	NR	NR	NR	NR	NR
Ligibel, 2016 <sup>14</sup>	NR	Arm 2	Exercise	Yes	Exercise sessions  Dose Moderate intensity, aerobic exercise program (goal 150 minutes/ week).  Frequency: In person meetings x 4 weeks, then monthly until 16 weeks. Plus telephone contacts and asked to practice at home (heart rate monitor, pedometer, exercise journal, local gym membership provided). Goal 150 minutes of moderate intensity exercise a week. Duration: Administered by Exercise physiologist	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
McMillan, 2007 <sup>15</sup>	KQ4	Arm 1	Standard care	Yes	General hospice care, routine education and support of caregivers as provided in hospice  Mode of administration: In-person  Dose  Frequency: Duration: Administered by Nurses, home health aides (received 4 day training)	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
McMillan, 2007 <sup>15</sup>	KQ4	Arm 2	Standard care and support	Yes	Standard care + Friendly visits from investigators or caregivers, discussing general feelings/ fears, providing support without formal training or intervention support  Mode of administration: In-person  Dose  Frequency: 3 visits in 9 days Duration: 45 minutes visit 1, then 30 minutes visit 2 and 3 Administered by Nurses, home health aides (received 4 day training)	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
McMillan, 2007 <sup>15</sup>	KQ4	Arm 3	Standard care and COPE	Yes	<p>Standard care + COPE</p> <p>Problem-based coping intervention, 4 phases: Creativity, Optimism, Planning, Expert Information to address specific needs.</p> <p>Encouraged problem solving, gave Home care guide for use, encouraged developed plans, called caregivers between visits to answer questions and provided their pager number.</p> <p>Mode of administration: Combination In person and over phone</p> <p>Dose</p> <p>Frequency: 3 visits in 9 days</p> <p>Duration: 45 minutes visit 1, then 30 minutes visit 2 and 3</p> <p>Administered by Nurses, home health aides (received 4 day training)</p>	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Molassiotis, 2015 <sup>16</sup>	KQ4	Arm 1	Control	Yes	<p>Routine care</p> <p>Mode of administration: In-person</p> <p>Dose Usual care: specialist nursing input, opioids, oxygen, use of other medical services, and also had home visits (same as experimental arm)</p> <p>Frequency: Duration: 12 weeks Administered: NR</p>	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Molassiotis, 2015 <sup>16</sup>	KQ4	Arm 2	Inspiratory muscle training (IMT)	Yes	<p>Inspiratory muscle training (IMT) via a pressure threshold device</p> <p>Mode of administration: In-person</p> <p>Dose Pressure setting variable, -7 to -41 (mean was -15) and then titrate by 2, coaching in person and then asked to do at home, monthly home visits to check/ coach. (cm of H2O)</p> <p>Frequency: 5 sessions/ week x 3-30 minutes/ session Duration: 12 weeks Administered: NR</p>	NR	NR		NR	NR
Moore, 2002 <sup>17</sup>	KQ4	Arm 1	Control	Yes	<p>Conventional care with outpatient appointments, usually every 2-3 months</p> <p>Mode of administration: In-person</p> <p>Dose</p> <p>Frequency: Duration: Administered by</p>	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Moore, 2002 <sup>17</sup>	KQ4	Arm 2	Nurse-led intervention	Yes	<p>Patients had access to nurse specialists for questions, symptoms by phone or in-person, rapid communication, regular contact and re-assurance, coordination of care</p> <p>Mode of administration: Combination In person and telephone</p> <p>Dose</p> <p>Frequency: As needed, average was 3 contacts/ month, 14% were initiated by patients, mean 23 minutes each encounter</p> <p>Duration: Administered by Clinical nurse specialist (trained for role by observing/ attending outpatient clinics)</p>	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Mosher, 2019 <sup>18</sup>	KQ4	Arm 1	Education/ support	Yes	<p>Orient to medical team, discuss quality of life, financial challenges, discuss health information on internet and books, review cancer information</p> <p>Mode of administration: Over phone</p> <p>Dose 6 x once weekly sessions, to both caregiver and patient</p> <p>Frequency: Weekly Duration: 50 minutes Administered by PhD student in clinical psychology with experience in psychoeducation</p>	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Mosher, 2019 <sup>18</sup>	KQ4	Arm 2	Acceptance and Commitment Therapy (ACT)	Yes	<p>Model of behavior change, coping strategy, mindfulness, perspective taking, cognitive diffusion, acceptance, values clarification (personal values), and plan/ practice value consistent actions</p> <p>Mode of administration: Over phone</p> <p>Dose 6 x once weekly sessions, to both caregiver and patient</p> <p>Frequency: Weekly Duration: 50 minutes Administered by Masters level social worker with experience in ACT</p>	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Nakano, 2020 <sup>19</sup>	NR	Arm 1	Non TENS	Yes	Usual care (not specified)  Dose Usual care and usual palliative care  Frequency: NR Duration: NR Administered by NR	NR	NR	NR	NR	Opioid Dose: NR Frequency: As needed Duration: NR Administered by NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Nakano, 2020 <sup>19</sup>	NR	Arm 2	TENS	Yes	<p>Transcutaneous electrical nerve stimulation (TENS)</p> <p>Dose TENS device had a 4-channel stimulator with four pairs of self-adhesive stimulating electrodes. Neurotomal pattern: one pair of gel pads on the back (pain), 2 pairs of gel pads on the back at the C7 to Th8 dermatomal level (nausea, vomiting, and dyspnea), 1 pair behind the medial malleolus (constipation). High-frequency (100 Hz) stimulation was used for all treatments except for constipation (10 Hz)</p> <p>Frequency: Once a day, x 5 days Duration: 30 minute session Administered by Physical therapist</p>	NR	NR	NR	NR	<p>Opioid Dose: NR Frequency: As needed Duration: NR Administered by NR</p>



Author, Year	Included in KQ4	Arm	Arm name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Nava, 2013 <sup>20</sup>	KQ4	Arm 1	Noninvasive ventilation (NIV)	Yes	NIV ventilator (bipap)  Mode of administration: In-person  Dose Start at 10/5 cm, increase by 2/1, rate set at 12/minute, (cm of H2O)  Frequency: Once, then continuous as tolerated Duration: 48 hours Administered: NR	NR	NR		NR	Morphine, subc Dose: 10 mg Frequency: As needed, and as needed every 4 hours to bring reduce dyspnea score by 1 AND to a level <=5. If needed, could also give 15 mg Duration: As needed during 48 hours



Author, Year	Included in KQ4	Arm	Arm Name	Patients adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Nava, 2013 <sup>20</sup>	KQ4	Arm 2	Oxygen	Yes	Oxygen  Mode of administration: In-person  Dose Oxygen via venturi mask or reservoir mask, goal O2 sat>90% (Liters)  Frequency: Once, then continuous as tolerated Duration: 48 hours Administered: NR	NR	NR		NR	Morphine, subc Dose: 10 mg Frequency: As needed, and as needed every 4 hours to bring reduce dyspnea score by 1 AND to a level <=5. If needed, could also give 15 mg Duration: As needed during 48 hours



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Philip, 2006 <sup>21</sup>	NR	Arm 1	Air first	Yes	Room air by nasal cannula  Mode of administration: In-person  Dose 4 Litre/ minute  Frequency: Once Duration: 15 minutes Administered: NR	NR	NR		NR	NR
Philip, 2006 <sup>21</sup>	NR	Arm 2	Oxygen first	Yes	Oxygen by nasal cannula  Mode of administration: In-person  Dose 4 Litre/ minute  Frequency: Once Duration: 15 minutes Administered: NR	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Ramirez, 2018 <sup>22</sup>	NR	Arm 1	Control	Yes	<p>Music therapist provides company and discusses music and preferences but without playing music</p> <p>Mode of administration: In-person</p> <p>Dose No music</p> <p>Frequency: Once Duration: 30 minutes Administered by Music therapist</p>	NR	NR	For music therapy, professional music therapists with extensive experience in palliative care.	NR	NR
Ramirez, 2018 <sup>22</sup>	NR	Arm 2	Music therapy	Yes	<p>Participants interviewed about music preferences, and instrumental/ vocal music played by music therapist</p> <p>Mode of administration: In-person</p> <p>Dose Choice of music played</p> <p>Frequency: Once Duration: 30 minutes Administered by Music therapist</p>	NR	NR	For music therapy, professional music therapists with extensive experience in palliative care.	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Rutkowski, 2019 <sup>23</sup>	NR	Arm 1	Control	Yes	Usual care (no exercise intervention)  Dose NR  Frequency: NR Duration: NR Administered by NR	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Rutkowski, 2019 <sup>23</sup>	NR	Arm 2	Exercise	Yes	<p>Exercise sessions</p> <p>Dose Each session had fitness (cycling or treadmill at 30-80% intensity of peak work rate), respiratory exercises (strengthening exercises for intercostal and diaphragm muscles, exhalation exercises, percussion therapy), for (30 minutes each ). Resistance exercise intensity 50-70% of the 1 repetition maximum. Nording walking for 45 minutes.</p> <p>Frequency: 5 sessions/ week for 2 weeks during weeks 2-3 of 3-week chemo cycles, for 2 chemo cycles. So for 4 out of total 6 weeks. Duration: Approx 2 hours per session Administered by Certified physiotherapist</p>	<p>Respiratory training</p> <p>Dose NR</p> <p>Frequency: NR Duration: NR Administered by NR</p>	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Ting, 2020 <sup>24</sup>	NR	Arm 1	Placebo	Yes	Dose Fan to unexposed leg  Frequency: NR Duration: 5 minutes Administered by NR	NR	NR	NR	NR	NR
Ting, 2020 <sup>24</sup>	NR	Arm 2	Fan on face	Yes	Dose Standing fan (ASAHI Fan Model PF-630) directed to blow air for 5 minutes across the region innervated by the second/third trigeminal nerve branches on one side of the face. The fan was directed toward one side of the face. Distance, location, side of face, strength, and swing of the fan was determined as per the patient's preference. Turned on at lowest speed and gently titrated up.  Frequency: NR Duration: 5 minutes Administered by NR	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Vanderbyl, 2017 <sup>25</sup>	KQ4	Arm 1	Standard exercise therapy	Yes	<p>Supervised exercise (cardiovascular + resistance) + hour walk at home daily</p> <p>Mode of administration: In-person</p> <p>Dose Group or individual sessions x 1 hour, Target 60-70% max heart rate and 2-4 METs, asked to walk at home for 1 hour daily</p> <p>Frequency: 2/ week Duration: 6 weeks Administered by Physiotherapists</p>	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Vanderbyl, 2017 <sup>25</sup>	KQ4	Arm 2	Qigong	Yes	<p>Supervised "walking qigong"- movement and breathing exercise, practice at home for 1 hour daily</p> <p>Mode of administration: In-person</p> <p>Dose Group sessions x 45 mins- walking exercise program, coordinated movement while meditating/ deep relaxation, breathing pattern is critical ("in, in, out"), asked to practice 1 hour at home daily</p> <p>Frequency: 2/ week Duration: 6 weeks Administered by Physiotherapists</p>	NR	NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Vickers, 2005 <sup>26</sup>	KQ4	Arm 1	Control	Yes	<p>Sham acupuncture needles (blunted needles) in body areas away from breathlessness sites</p> <p>Mode of administration: In-person</p> <p>Dose</p> <p>Frequency: Once Duration: 15 minutes Administered by Licensed acupuncturists</p>	<p>Sham acupressure studs inserted 1 hour after removal of acupuncture needles- -patients rub approx 3x/ day at home x 1 week</p> <p>Mode of administration: Combination In person, at home</p> <p>Dose</p> <p>Frequency: Placed once in person, patients rub 3x/ day at home Duration: 1 week Administered by Licensed acupuncturists</p>	NR	<p>Study acupuncturists are certified by the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) and are licensed to practice in New York State. Clinical experience, 3 – 25 years, including with cancer patients.</p>	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Vickers, 2005 <sup>26</sup>	KQ4	Arm 2	Acupuncture/ acupressure	Yes	<p>True acupuncture needles to depth of 0.5-1.5 cm (including auricular points) at breathlessness sites, elicit de qi, no movement after placing needles</p> <p>Mode of administration: In-person</p> <p>Dose</p> <p>Frequency: Once Duration: 15 minutes Administered by Licensed acupuncturists</p>	<p>Stainless steel acupressure syuds applied, placed in person, patients rub approx 3x/ day at home x 1 week</p> <p>Mode of administration: Combination In person, at home</p> <p>Dose</p> <p>Frequency: Placed once in person, patients rub 3x/ day at home Duration: 1 week Administered by Licensed acupuncturists</p>	NR	<p>Study acupuncturists are certified by the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) and are licensed to practice in New York State. Clinical experience, 3 – 25 years, including with cancer patients.</p>	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Wong, 2017 <sup>27</sup>	NR	Arm 1	Control	Yes	Same nursing, oxygen, rescue meds, posture change as usual care, plus caregivers present  Mode of administration: In-person  Dose Accompanied by caregivers  Frequency: Once Duration: 5 minutes Administered: NR	NR	NR		NR	NR
Wong, 2017 <sup>27</sup>	NR	Arm 2	Fan	Yes	Desk fan to face  Mode of administration: In-person  Dose 9 inch fan blade, electric fan, low air speed to start, distance from face per patient preference  Frequency: Once Duration: 5 minutes Administered: NR	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 1	Control	Yes	Standard care  Mode of administration: In-person  Dose  Frequency: Duration: Administered by Usual care	NR	NR		NR	NR
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 2	Lay foot manipulation	Yes	Superficially similar to reflexology but avoided the 9 zones and deep thumb pressure  Mode of administration: In-person  Dose  Frequency: 4 x once Weekly Duration: 30 minutes each x 4 sessions Administered by Lay women	NR	NR	LFM providers were laywomen who were naive to reflexology and trained in the LFM protocol by the study education coordinator	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Wyatt, 2012 <sup>28</sup>	KQ4	Arm 3	Reflexology	Yes	<p>Stimulation of 9 essential breast cancer specific reflexes-- deep thumb walking pressure</p> <p>Mode of administration: In-person</p> <p>Dose</p> <p>Frequency: 4 x once Weekly Duration: 30 minutes each x 4 sessions Administered by Certified reflexologists</p>	NR	NR	Reflexology providers were certified reflexologists through the Ingham method of reflexology and trained by the study's lead reflexologist, who had 22 years of experience.	NR	NR
Yorke, 2015 <sup>29</sup>	KQ4	Arm 1	Usual care	Yes	<p>No other info given</p> <p>Mode of administration: In-person</p> <p>Dose</p> <p>Frequency: Duration: Administered by</p>	NR	NR		NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Intervention 3	For Integrative Medicine Interventions, Instructor Qualifications/ Training	Breakthrough	Rescue Therapy
Yorke, 2015 <sup>29</sup>	KQ4	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	Yes	<p>Controlled breathing technique, and cough easing technique (exercise, warning signs, modified swallowing)</p> <p>Mode of administration: Combination In person and over phone and at home</p> <p>Dose Education face to face, and over telephone</p> <p>Frequency: Once in person, then repeat in person after 1 week, telephone follow-up at week 3, practice breathing exercises twice daily at home</p> <p>Duration: 1 hour (combined for all interventions)</p> <p>Administered by Nurses, physiotherapists, complimentary therapists (underwent 3 hour face to face training and refresher course half-way through trial)</p>	<p>Acupressure to hand, wrist, sternum, knee,</p> <p>Mode of administration: Combination In person training, patients apply pressure themselves</p> <p>Dose</p> <p>Frequency: At least twice daily Duration: 1 minute Administered by Trained complimentary therapists (underwent 3 hour face to face training and refresher course half-way through trial)</p>	<p>Information pack-practical advice, communication strategy, sleep hygiene, energy conservation, anxiety management, caregiver support. Psycho-educational counselling for internalizing locus of control, acceptance that it is hard, and setting realistic goals.</p> <p>Mode of administration: Combination In person training, patients practice on own</p>	For acupressure, trained complementary therapists received specific training to deliver the intervention (One face-to-face group session lasting 3 hours, and a follow-up refresher session half way through the trial)	NR	NR

ACBT= active cycle of breathing; ACT= Acceptance and Commitment Therapy; BIS= breathlessness intervention service; CD=compact disk; HR=heart rate; KQ4=Key Question 4; LFM=lay foot manipulation; NR=not reported



**Evidence Table D-14. Intervention characteristics for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Aabom, 2019 <sup>30</sup>	NR	Arm 1	Red morphine drops	Yes	Dose: Opioid- naïve: 5mg, Opioid-treated: 10mg Frequency: Once Duration: Given one time	NR	NR	NR
Aabom, 2019 <sup>30</sup>	NR	Arm 2	Morphine sulfate	Yes	Dose: Opioid- naïve: 5mg, Opioid-treated: 10mg Frequency: Once Duration: Given one time	NR	NR	NR
Allard, 1999 <sup>31</sup>	NR	Arm 1	Opioid dose 25% of 4 hourly regular dose	NR	Opioid (not specified) Mode of administration: Oral or subcutaneous (depending on regular scheduled regimen)  Planned Dose: Opioid dose 25% of 4 hourly regular current dose NR Frequency: Once Duration: Once  Titration NR	NR	Patients were given breakthrough, but no specified Dose: NR Frequency: NR Duration: NR	Rescue therapy available, not specified Dose: NR Frequency: NR Duration: NR
Allard, 1999 <sup>31</sup>	NR	Arm 2	Opioid dose 50% of 4 hourly regular dose	NR	Opioid (not specified) Mode of administration: Oral or subcutaneous (depending on regular scheduled regimen)  Planned Dose: Opioid dose 50% of 4 hourly regular current dose Frequency: Once Duration: Once  Titration NR	NR	Patients were given breakthrough, but no specified Dose: NR Frequency: NR Duration: NR	Rescue therapy available, not specified Dose: NR Frequency: NR Duration: NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Bruera, 1993 <sup>32</sup>	NR	Arm 1	Placebo	Yes	Dose Mean: NR Median: NR Range: NR Maximum: NR  Frequency: Once  Duration: Given one time	NR	NR	NR
Bruera, 1993 <sup>32</sup>	NR	Arm 2	Morphine	Yes	Dose Mean: 34mg (SD 12mg) Median: NR Range: NR Maximum: NR  Frequency: Once  Duration: Given one time	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Bruera, 2005 <sup>33</sup>	KQ4	Arm 1	Subcutaneous morphine	NR	Morphine Mode of administration: Subcutaneous  Planned NR  Titration Dose Mean: NR Median: 45mg Range: 7.5 to 200mg Maximum: NR  Frequency: Once  Duration: Once	Normal saline Mode of administration: Nebulized NR  Planned Dose: NR Frequency: Once Duration: Once  Titration NR	NR	NR
Bruera, 2005 <sup>33</sup>	KQ4	Arm 2	Nebulized morphine	NR	Morphine Mode of administration: Nebulized  Planned NR  Titration Dose Mean: NR Median: 45mg Range: 7.5 to 200mg Maximum: NR  Frequency: Once  Duration: Once	Normal saline Mode of administration: Subcutaneous NR  Planned Dose: 3 cc Frequency: Once Duration: Once  Titration NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Charles, 2008 <sup>34</sup>	KQ4	Arm 1	Nebulized saline	NR	Saline Mode of administration: Nebulized  Planned Dose: 3 ml Frequency: Once Duration: NR  Titration NR	Sterilized water Mode of administration: Other-specify Oral or subcutaneous  Planned NR  Titration NR	Offered (drugs not specified) Dose: NR Frequency: NR Duration: NR	NR
Charles, 2008 <sup>34</sup>	KQ4	Arm 2	Nebulized hydromorphone	NR	Hydromorphone Mode of administration: Nebulized  Planned Dose: 5 mg Frequency: Once Duration: NR  Titration NR	Sterilized water Mode of administration: Other-specify Oral or subcutaneous  Planned NR  Titration NR	Offered (drugs not specified) Dose: NR Frequency: NR Duration: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Charles, 2008 <sup>34</sup>	KQ4	Arm 3	Systemic hydromorphone	NR	<p>Hydromorphone Mode of administration: Systemic (Oral or subcutaneous)</p> <p>Planned Dose: NR Frequency: Once Duration: NR</p> <p>Titration NR</p>	<p>Saline Mode of administration: Nebulized NR</p> <p>Planned Dose: 3 ml Frequency: NR Duration: NR</p> <p>Titration NR</p>	Offered (drugs not specified) Dose: NR Frequency: NR Duration: NR	NR
Gamborg, 2013 <sup>35</sup>	KQ4	Arm 1	Red Morphine Drops	NR	<p>Red morphine drops Mode of administration: Oral</p> <p>Planned NR</p> <p>Titration Dose Mean: NR Median: 8.2percent of their total 24 hours opioid consumption Range: 3.3 to 8.6percent of their total 24 hours opioid consumption Maximum: 24mgpercent of their total 24 hours opioid consumption</p> <p>Frequency: NR</p> <p>Duration: 1 hour</p>	<p>Isotonic saline Mode of administration: Subcutaneous NR</p> <p>Planned NR</p> <p>Titration NR</p>	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Gamborg, 2013 <sup>35</sup>	KQ4	Arm 2	Subcutaneous Morphine	NR	<p>Subcutaneous morphine Mode of administration: Subcutaneous</p> <p>Planned NR</p> <p>Titration Dose Mean: percent of their total 24 hours opioid consumption Median: 5percent of their total 24 hours opioid consumption Range: 1.5 to 5.5percent of their total 24 hours opioid consumption Maximum: 14.4mgpercent of their total 24 hours opioid consumption</p> <p>Frequency: NR</p> <p>Duration: 1 hour</p>	<p>Placebo drops Mode of administration: Oral NR</p> <p>Planned NR</p> <p>Titration Dose Mean: NR Median: NR Range: NR Maximum: 40drops</p> <p>Frequency: NR</p> <p>Duration: NR</p>	NR	NR
Hardy, 2016 <sup>36</sup>	KQ4	Arm 1	Placebo	NR	<p>Citric acid in normal saline Mode of administration: Intranasal spray</p> <p>Planned Dose: 1.5 mg/spray Frequency: As needed, no more than every 4 hours Duration: Max 14 days</p> <p>Titration NR</p>	NR	Opioids (not specified) Dose: NR Frequency: NR Duration: NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Hardy, 2016 <sup>36</sup>	KQ4	Arm 2	Midazolam hydrochloride	NR	<p>Midazolam hydrochloride Mode of administration: Intranasal spray</p> <p>Planned Dose: 1.5 mg/spray Frequency: As needed, no more than every 4 hours Duration: Max 14 days</p> <p>Titration NR</p>	NR	Opioids (not specified) Dose: NR Frequency: NR Duration: NR	NR
Hui, 2014 <sup>37</sup>	KQ4	Arm 1	Placebo	Yes	<p>0.9% sodium chloride Mode of administration: Subcutaneous</p> <p>Planned Dose: NR Frequency: Single dose Duration: NR</p> <p>Titration NR</p>	NR	NR	NR
Hui, 2014 <sup>37</sup>	KQ4	Arm 2	Fentanyl	Yes	<p>Fentanyl Mode of administration: Subcutaneous</p> <p>Planned Dose: 30 to 350 mcg Frequency: Single dose Duration: NR</p> <p>Titration NR</p>	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Hui, 2016 <sup>38</sup>	KQ4	Arm 1	Placebo	NR	Placebo Mode of administration: Nasal spray  Planned NR  Titration Dose Mean: NR Median: NR Range: NR Maximum: NR  Frequency: One dose after first walk (max 1 hour after), second dose after second walk (max 1 hour after)  Duration: 2 hours	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Hui, 2016 <sup>38</sup>	KQ4	Arm 2	FPNS	NR	<p>Fentanyl Pectin Mode of administration: Nasal spray</p> <p>Planned NR</p> <p>Titration Dose Mean: NR Median: NR Range: 100 to 400mcg Maximum: 400mcg</p> <p>Frequency: One dose after first walk (max 1 hour after), second dose after second walk (max 1 hour after)</p> <p>Duration: 2 hours</p>	NR	NR	NR
Hui, 2016 <sup>39</sup>	KQ4	Arm 1	Placebo	NR	<p>Not specified Mode of administration: Oral</p> <p>Planned Dose: Day 1-4: placebo, Day 5-14: placebo Frequency: twice daily Duration: 14 days</p> <p>Titration NR</p>	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Hui, 2016 <sup>39</sup>	KQ4	Arm 2	Dexamethasone	NR	Dexamethasone Mode of administration: Oral  Planned Dose: Day 1-4: 8mg, Day 5-14: 4mg mg Frequency: twice daily Duration: 14 days  Titration NR	NR	NR	NR
Hui, 2017 <sup>40</sup>	KQ4	Arm 1	Placebo	NR	Placebo effervescent tablets Mode of administration: Oral  Planned Dose: NR Frequency: Once Duration: Once  Titration NR	NR	NR	NR
Hui, 2017 <sup>40</sup>	KQ4	Arm 2	FBT	NR	Fentanyl Mode of administration: Buccal  Planned Dose: Patients with MEDD 60-65mg/day, received 100mcg fentanyl. For patients with 66-130mg/day, received 200mcg fentanyl. Frequency: Once Duration: Once  Titration NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Hui, 2019 <sup>41</sup>	KQ4	Arm 1	High dose fentanyl	NR	Fentanyl Mode of administration: Sublingual  Planned Dose: 35%-45% of MEDD, 200 to 800mcg Frequency: Once Duration: 1 day  Titration NR	NR	NR	NR
Hui, 2019 <sup>41</sup>	KQ4	Arm 2	Low dose fentanyl	NR	Fentanyl Mode of administration: Sublingual  Planned Dose: 15%-25% of MEDD, 100 to 400mcg Frequency: Once Duration: 1 day  Titration NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Kawabata, 2013 <sup>42</sup>	KQ4	Overall	Overall	Yes	<p>Oxycodone hydrochloride Mode of administration: Subcutaneous</p> <p>Planned NR</p> <p>Titration Dose Mean: 44.6mg/d Median: NR/d Range: 5.5 to 206.6mg/d Maximum: NR/d</p> <p>Frequency: NR</p> <p>Duration: 2.08 to 111.2 days (average 14.4 days)</p>	<p>Hydrocotarnine hydrochloride Mode of administration: Subcutaneous NR</p> <p>Planned NR</p> <p>Titration Dose Mean: 44.6mg/d Median: NRmg/d Range: 5.5 to 206.6mg/d Maximum: NRmg/d</p> <p>Frequency: NR</p> <p>Duration: 2.08 to 111.2 days (average 14.4 days)</p>	NR	<p>Oxycodone hydrochloride and hydrocotarnine hydrochloride Dose: 8mg of oxycodone, 2mg hydrocotarnine Frequency: NR Duration: NR</p>
Navigante, 2006 <sup>43</sup>	KQ4	Arm 1	Morphine	NR	<p>Morphine Mode of administration: Subcutaneous</p> <p>Planned Dose: 2.5mg or a 25% increment above the DsEDM for those receiving baseline opioids mg Frequency: Every 4 hours Duration: 48 hours</p> <p>Titration NR</p>	NR	NR	<p>Midazolam Dose: 5mg Frequency: 15 min PRN Duration: NR</p>



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Navigante, 2006 <sup>43</sup>	KQ4	Arm 2	Midazolam	NR	<p>Midazolam Mode of administration: Subcutaneous</p> <p>Planned Dose: 5 mg Frequency: Every 4 hours Duration: 48 hours</p> <p>Titration NR</p>	NR	NR	<p>Morphine Dose: 2.5mg Frequency: 15 min PRN Duration: NR</p>
Navigante, 2006 <sup>43</sup>	KQ4	Arm 3	Morphine+Midazolam	NR	<p>Morphine Mode of administration: Subcutaneous</p> <p>Planned Dose: 2.5mg or a 25% increment above the DsEDM for those receiving baseline opioids mg Frequency: Every 4 hours Duration: 48 hours</p> <p>Titration NR</p>	<p>Midazolam Mode of administration: Subcutaneous NR</p> <p>Planned Dose: 5 mg Frequency: Every 4 hours Duration: 48 hours</p> <p>Titration NR</p>	NR	<p>Morphine Dose: 2.5mg Frequency: 15 min PRN Duration: NR</p>



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Navigante, 2010 <sup>44</sup>	KQ4	Arm 1	Morphine	29 (96.7)	Morphine Mode of administration: Oral  Planned NR  Titration Dose Mean: NR Median: NR Range: The dose that reduced the intensity of dyspnea ≥ 50% (minimum 3mg starting dose) Maximum: NR  Frequency: Every 4 waking hours  Duration: 5 days	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Navigante, 2010 <sup>44</sup>	KQ4	Arm 2	Midazolam	30 (96.8)	<p>Midazolam Mode of administration: Oral</p> <p>Planned NR</p> <p>Titration Dose Mean: NR Median: NR Range: The dose that reduced the intensity of dyspnea <math>\geq</math> 50% (minimum 2mg starting dose) Maximum: NR</p> <p>Frequency: Every 4 waking hours</p> <p>Duration: 5 days</p>	NR	NR	NR
Peoples, 2016 <sup>45</sup>	NR	Arm 1	Placebo	NR	<p>Not specified Mode of administration: Oral</p> <p>Planned Dose: 1 capsule Frequency: Day 1-3: bedtime, Day 4-28: morning and bedtime Duration: 28 days</p> <p>Titration NR</p>	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Peoples, 2016 <sup>45</sup>	NR	Arm 2	Buspirone	NR	Buspirone Mode of administration: Oral  Planned Dose: 10 mg Frequency: Day 1-3: p.o. bedtime, Day 4-28: morning and bedtime Duration: 28 days  Titration NR	NR	NR	NR
Pinna, 2015 <sup>46</sup>	KQ4	Arm 1	Placebo	Yes	Placebo, not specified Mode of administration: NR  Planned Dose: Previously receiving opioids: 200ug, Not previously receiving opioids: 400ug Frequency: Once Duration: 1 day  Titration NR	NR	NR	NR
Pinna, 2015 <sup>46</sup>	KQ4	Arm 2	Fentanyl citrate	Yes	Fentanyl citrate Mode of administration: Oral transmucosal  Planned Dose: Previously receiving opioids: 200ug, Not previously receiving opioids: 400ug ug Frequency: Once Duration: 1 day  Titration NR	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Simon, 2016 <sup>47</sup>	NR	Arm 1	Immediate release morphine	No	Dose Mean: NR Median: NR Range: 16.7% to 116.7% daily oral morphine equivalent Maximum: 116.7%  Frequency: maximum 8 doses  Duration: 2 days	NR	NR	NR
Simon, 2016 <sup>47</sup>	NR	Arm 2	Fentanyl buccal tablet	No	Dose Mean: NR Median: NR Range: 100ug to 600ug Maximum: 600ug  Frequency: maximum 8 doses  Duration: 2 days	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Tian, 2016 <sup>48</sup>	KQ4	Arm 1	Morphine	NR	Morphine Mode of administration: Subcutaneous  Planned Dose: 5mg or 10% of total opioid use in last 24 hours mg Frequency: Once Duration: 1 day  Titration NR	NR	NR	NR
Tian, 2016 <sup>48</sup>	KQ4	Arm 2	Methylprednisolone	NR	Methylprednisolone, in 100 normal saline Mode of administration: IV  Planned Dose: 40 mg Frequency: Once Duration: Dripped for 30min, 1 day  Titration NR	NR	NR	NR
Tian, 2016 <sup>48</sup>	KQ4	Arm 3	Aminophylline	NR	Aminophylline, in 5% glucose Mode of administration: IV  Planned Dose: 0.25 g Frequency: Once Duration: Dripped for 30min, 1 day  Titration NR	NR	NR	NR

DsEDM= daily subcutaneous equivalent dose of morphine; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; KQ4=Key Question 4; MEDD= morphine equivalent daily dose; n=population; NR=not reported; PRN= pro re nata



**Evidence Table D-15. Intervention characteristics for studies comparing combination non-pharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Gottlieb, 2020 <sup>49</sup>	NR	Arm 1	Control	Yes	Informed of COPD diagnosis if newly diagnosed at screening and asked to schedule follow-up with general practitioner, no medication changes actively.	NR	NR	NR
Gottlieb, 2020 <sup>49</sup>	NR	Arm 2	Intervention	Yes	Three in-person visits with a pulmonary physician at baseline, 12 weeks, and 24 weeks. If minimal symptoms, telephone follow-up also acceptable. Patients could call clinic with questions. Pulmonary physician assessed COPD severity (GOLD classification) and need for change in medications. Patients counseled. Correct inhalation technique verified.	NR	NR	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Minchom, 2016 <sup>50</sup>	KQ4	Arm 1	Acupuncture	NR	<p>Acupuncture Mode of administration: Acupuncture</p> <p>Planned In-person</p> <p>Titration Dose 30mm acupuncture needles (Seirin) were inserted and left in situ for 10 min. NR</p> <p>Frequency: NR Duration: NR Administered by NR</p>	<p>Morphine Mode of administration: Oral</p> <p>Planned Dose: NR Frequency: As needed Duration: 14 days</p> <p>Titration NR</p>	<p>Morphine with anti-emetics and laxatives Dose: NR Frequency: NR Duration: NR</p>	NR
Minchom, 2016 <sup>50</sup>	KQ4	Arm 2	Morphine	NR	<p>Morphine Mode of administration: Oral</p> <p>Planned Dose: 2.5 mg Frequency: every 4 hours Duration: 14 days</p> <p>Titration NR</p>	<p>Mode of administration:</p> <p>Planned</p> <p>Titration</p>	<p>Morphine with anti-emetics and laxatives Dose: 2.5 Frequency: every 1 hour as needed Duration: 14 days</p>	NR



Author, Year	Included in KQ4	Arm	Arm Name	Patients Adhering to Treatment, n (%)	Intervention 1	Intervention 2	Breakthrough	Rescue Therapy
Minchom, 2016 <sup>50</sup>	KQ4	Arm 3	Acupuncture+Morphine	NR	Acupuncture Mode of administration: Acupuncture  Planned In-person  Titration Dose 30mm acupuncture needles (Seirin) were inserted and left in situ for 10 min. NR  Frequency: NR Duration: NR Administered by NR	Morphine Mode of administration: Oral  Planned Dose: 2.5 mg Frequency: 20 min before acupuncture Duration: 14 days  Titration NR	Morphine with anti-emetics and laxatives Dose: NR Frequency: NR Duration: NR	NR

COPD= Chronic obstructive pulmonary disease; KQ4=Key Question 4; n=population; NR=not reported



**Evidence Table D-16. Anxiety continuous outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Vanderbyl, 2017 <sup>25</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Standard exercise therapy	Mean change in anxiety, baseline to week 6	HADS- anxiety scale	Final: 6 weeks	Baseline: 13 Followup: 13	Baseline: Mean 4.9 (SD 3.6) Followup: NR	Mean change from baseline: - 0.4 (SD 3.3), p=NR	Comparator: Standard exercise therapy Difference in mean: p=0.82 SMD: -0.071 (95% CI: -0.87 to 0.73)	NR	For between group analysis- only p value given
	Arm 2	Qigong	Mean change in anxiety, baseline to week 6	HADS- anxiety scale	Final: 6 weeks	Baseline: 11 Followup: 11	Baseline: Mean 6.1 (SD 3.5) Followup: NR	Mean change from baseline: - 0.6 (SD 2.1), p=NR	NA	NR	
Mosher, 2019 <sup>18</sup> Behavioral/Psych vs Behavioral/Psych+ Integrative medicine interventions	Arm 1	Education/ support	Mean change in anxiety, baseline to 6 weeks	PROMIS	Final: 6 weeks; Primary: 2 weeks	Baseline: 25 Followup: 18 Primary FU: 18	Baseline: Mean 7.69 (SE 0.72) Followup: Mean 7.24 (SE 0.76) Primary Followup: Mean 7.54 (SE 0.76)	NR	Comparator: Education/ support Difference in mean: p=0.99 SMD: 0.011 (95% CI: - 0.54 to 0.57)	NR	
	Arm 2	Acceptance and Commitme nt Therapy (ACT)	Mean change in anxiety, baseline to 6 weeks	PROMIS	Final: 6 weeks; Primary: 2 weeks	Baseline: 25 Followup: 20 Primary FU: 20	Baseline: Mean 6.36 (SE 0.72) Followup: Mean 5.95 (SE 0.74) Primary Followup: Mean 6.26 (SE 0.74)	NR	NA	NR	
Ramirez, 2018 <sup>22</sup> Placebo vs Integrative medicine interventions	Arm 1	Control	Mean change in anxiety, baseline to 30 minutes	ESAS	Final: 30 minutes	Baseline: 20 Followup: 20	Baseline: NR Followup: NR	Mean change from baseline: NR, p=NS	NA	Group effect, time effect	
	Arm 2	Music therapy	Mean change in anxiety, baseline to 30 minutes	ESAS	Final: 30 minutes	Baseline: 20 Followup: 20	Baseline: NR Followup: NR	Mean change from baseline: NR, p=0.002	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kako, 2018 <sup>13</sup> Placebo vs Integrative medicine interventions	Arm 1	Fan to legs (control)	Mean change in anxiety, baseline to 5 minutes,	ESAS-R	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 3.45 (SD 2.72) Followup: NR	Mean change from baseline: - 0.15 (SD NR), (95% CI: -0.66, 0.36), p=NR	Comparator: Control Difference in mean: p=0.706 SMD: -0.11 (95% CI: - 0.73 to 0.51)	NR	Music therapy improved dyspnea and anxiety in music arm, not in control arm.
	Arm 2	Fan to face	Mean change in anxiety, baseline to 5 minutes,	ESAS-R	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 3.9 (SD 3.18) Followup: NR	Mean change from baseline: - 0.25 (SD NR), (95% CI: -0.45, - 0.04), p=NR	NA	NR	
Corner, 1996 <sup>6</sup> Usual care vs Activity/Rehab+ Behavioral/Psych	Arm 1	Control	Median change in anxiety, baseline to 12 weeks	HADS- anxiety scale	Final: 12 weeks	Baseline: 9 Followup: 9	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), (95% CI: -1, 3), p=NR	Comparator: Control Difference in medians: p=NS	NR	
	Arm 2	Nurse led intervention	Median change in anxiety, baseline to 12 weeks	HADS- anxiety scale	Final: 12 weeks	Baseline: 11 Followup: 11	Baseline: NR Followup: NR	Median change from baseline: 1.5 (SD NR), (95% CI: 0-5), p=NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Farquhar, 2014 <sup>9</sup> Usual care vs Activity/Rehab+ Behavioral/Psych+ Integrative medicine interventions	Arm 1	Control	Mean change in anxiety, baseline to 2 weeks	HADS- anxiety scale	Final: 2 weeks	Baseline: 26 Followup: 26	Baseline: Mean 7.88 (SD 3.41) Followup: Mean 7.85 (SD 3.59)	NR	Comparator: Intervention Difference in mean : 0.017 (SD NR) (95% CI: -1.52, 1.56), p=0.98 SMD: 0.02 (95% CI: - 0.51 to 0.56)	Baseline value	
	Arm 2	Intervention	Mean change in anxiety, baseline to 2 weeks	HADS- anxiety scale	Final: 2 weeks	Baseline: 28 Followup: 28	Baseline: Mean 7 (SD 4.08) Followup: Mean 7.07 (SD 5.05)	NR	NA	NR	
Yorke, 2015 <sup>29</sup> Usual care vs Activity/Rehab+ Behavioral/Psych+ Integrative medicine interventions	Arm 1	Usual care	Mean change in anxiety, baseline to week 12	HADS- anxiety scale	Final: 12 weeks	Baseline: 51 Followup: 40	Baseline: NR Followup: NR	Mean change from baseline: - 0.06 (SD 3.1), p=NR	Comparator: Respiratory Distress Symptom Intervention (RDSI) Difference in mean : 0.25 (SD 0.97) (95% CI: -1.66, 2.15), p=0.8 SMD: 0.30 (95% CI: - 0.10 to 0.69)	Group effect, time effect, interactio n	
	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	Mean change in anxiety, baseline to week 12	HADS- anxiety scale	Final: 12 weeks	Baseline: 50 Followup: 31	Baseline: NR Followup: NR	Mean change from baseline: 0.81 (SD 2.75), p=NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Corner, 1996 <sup>6</sup> Usual care vs Behavioral/Psych+ Activity/Rehab	Arm 1	Control	Median change in anxiety, baseline to 12 weeks	HADS- anxiety scale	Final: 12 weeks	Baseline: 9 Followup: 9	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), (95% CI: -1 to 3), p=NR	Comparator: Control Difference in medians: p=NS	NR	
	Arm 2	Nurse led intervention	Median change in anxiety, baseline to 12 weeks	HADS- anxiety scale	Final: 12 weeks	Baseline: 11 Followup: 11	Baseline: NR Followup: NR	Median change from baseline: 1.5 (SD NR), (95% CI: 0 to 5), p=NR	NR	NR	
Chan, 2011 <sup>5</sup> Usual care vs Behavioral/Psych+ Activity/Rehab	Arm 1	Control	Mean change in anxiety, baseline to 12 weeks	A-state scale of the State- Trait Anxiety Inventory (20-80)	Final: 12 weeks; Primary: 6 weeks	Baseline: 70 Followup: 40 Primary FU: 59	Baseline: Mean 43.24 (SD 10.59) Followup: Mean 40.65 (SD 11.3) Primary Followup: Mean 44.54 (SD 11.95)	NR	Comparator: p=0.005 SMD: -0.04 (95% CI: - 0.37 to 0.29)	Time point, group, stage of cancer	
	Arm 2	Psychoedu cational intervention (PEI)	Mean change in anxiety, baseline to 12 weeks	A-state scale of the State- Trait Anxiety Inventory (20-80)	Final: 12 weeks; Primary: 6 weeks	Baseline: 70 Followup: 62 Primary FU: 68	Baseline: Mean 42.83 (SD 10.4) Followup: Mean 39.8 (SD 10.36) Primary Followup: Mean 39.25 (SD 10.24)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Dhillon, 2017 <sup>7</sup> Usual care vs Behavioral/Psych+ Activity/Rehab	Arm 1	Usual care	Mean change in anxiety	General Health Questionn aire-12	Final: 6 months; Primary: 2 months	Baseline: 55 Followup: 27 Primary FU: 42	Baseline: Mean 23.63 (NR) Followup: Mean 22.47 (NR) Primary Followup: Mean 23.52 (NR)	NR	Ref	NR	
	Arm 2	Exercise	Mean change in anxiety	General Health Questionn aire-12	Final: 6 months; Primary: 2 months	Baseline: 56 Followup: 35 Primary FU: 48	Baseline: Mean 25.06 (NR) Followup: Mean 23.68 (NR) Primary Followup: Mean 22.72 (NR)	NR	Comparator: Arm1 Difference in mean : At 2 months: -0.8 (95% CI: -3.24 to 1.64), p=0.521	NR	
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative Medicine Interventions vs Integrative Medicine Interventions	Arm 2	Lay foot manipulatio n	Mean change in anxiety, baseline to 11 weeks	State-Trait Anxiety Inventory (0-60)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 67 Primary FU: 76	Baseline: Mean 34.9 (SD 11.1) Followup: Mean 33.3 (SD 10.7) Primary Followup: Mean 32.5 (SD 10.2)	NR	NR SMD: -0.22 (95% CI: - 0.51 to 0.06)	Baseline anxiety and depressi on score	
	Arm 3	Reflexology	Mean change in anxiety, baseline to 11 weeks	State-Trait Anxiety Inventory (0-60)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 71 Primary FU: 75	Baseline: Mean 39.6 (SD 13.1) Followup: Mean 35.4 (SD 11.1) Primary Followup: Mean 37.7 (SD 13.3)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative Medicine Interventions	Arm 1	Control	Mean change in anxiety, baseline to 11 weeks	State-Trait Anxiety Inventory (0-60)	Final: 11 weeks; Primary: 5 weeks	Baseline: 96 Followup: 63 Primary FU: 71	Baseline: Mean 34.3 (SD 12.6) Followup: Mean 34.1 (SD 12.1) Primary Followup: Mean 34.1 (SD 10.6)	NR	NR SMD: -0.33 (95% CI: - 0.61 to -0.04)	NR	
	Arm 3	Reflexology	Mean change in anxiety, baseline to 11 weeks	State-Trait Anxiety Inventory (0-60)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 71 Primary FU: 75	Baseline: Mean 39.6 (SD 13.1) Followup: Mean 35.4 (SD 11.1) Primary Followup: Mean 37.7 (SD 13.3)	NR	NA	NR	
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative Medicine Interventions	Arm 1	Control	Mean change in anxiety, baseline to 11 weeks	State-Trait Anxiety Inventory (0-60)	Final: 11 weeks; Primary: 5 weeks	Baseline: 96 Followup: 63 Primary FU: 71	Baseline: Mean 34.3 (SD 12.6) Followup: Mean 34.1 (SD 12.1) Primary Followup: Mean 34.1 (SD 10.6)	NR	NR SMD: -0.13 (95% CI: - 0.40 to 0.16)	NR	
	Arm 2	Lay foot manipulation	Mean change in anxiety, baseline to 11 weeks	State-Trait Anxiety Inventory (0-60)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 67 Primary FU: 76	Baseline: Mean 34.9 (SD 11.1) Followup: Mean 33.3 (SD 10.7) Primary Followup: Mean 32.5 (SD 10.2)	NR	NA	Baseline anxiety and depression score	
Molassiotis, 2015 <sup>16</sup> Usual care vs Activity/Rehab	Arm 1	Control	Mean change in anxiety, baseline to week 12	HADS- anxiety scale	Final: 12 weeks	Baseline: 23 Followup: 18	Baseline: NR Followup: NR	NR	Comparator: Control Difference in mean: p=0.027	NR	Only follow up point estimates given, no comparison/ p value
	Arm 2	Inspiratory muscle training (IMT)	Mean change in anxiety, baseline to week 12	HADS- anxiety scale	Final: 12 weeks	Baseline: 24 Followup: 18	Baseline: NR Followup: NR	NR	NA	NR	

CI=confidence interval; ESAS= Edmonton Symptom Assessment Scale; HADS= Hospital Anxiety and Depression Scale (HADS); N=sample size; NR=not reported; NS=non-significant; p=p-value; PEI= Psychoeducational intervention; PROMIS= Patient-Reported Outcomes Measurement Information System; RCT=randomized clinical trial; RDSI= Respiratory Distress Symptom Intervention; SE=standard error; SMD=standardized mean difference



**Evidence Table D-17. Breathlessness continuous outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 1993 <sup>3</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Air first	Mean change in dyspnea (at best), baseline to 5 minutes	VAS (0- 100)	Final: 5 minutes	Baseline: 14 Followup: 14	Baseline: NR Followup: NR	NR	Comparator: Air Difference in mean : 20.5 (SD NR) (95% CI: 13.5, 27.6), p<0.001	Time point, group, stage of cancer	
	Arm 2	Oxygen first	Mean change in dyspnea (at best), baseline to 5 minutes	VAS (0- 100)	Final: 5 minutes	Baseline: 14 Followup: 14	Baseline: NR Followup: NR	NR	NR	NR	
Henke, 2014 <sup>10</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Control	Mean change in dyspnea	EORTC QLQ-C30	Final: 9 weeks	Baseline: 11 Followup: 11	Baseline: Mean 64.1 (SD 34.59) Followup: Mean 51.28 (SD35)	NR	Comparator: Control Difference in mean : p<0.05 SMD: 0.35 (95% CI: - 0.41 to 1.1)	NR	
	Arm 2	Intervention	Mean change in dyspnea	EORTC QLQ-C30	Final: 9 weeks	Baseline: 18 Followup: 18	Baseline: Mean 37.5 (SD 23.96) Followup: Mean 35.42 (SD30.96)	NR	NA	NR	
Vanderbyl, 2017 <sup>25</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Standard exercise therapy	Mean change in dyspnea, baseline to week 6	FACT-G	Final: 6 weeks	Baseline: 13 Followup: 13	Baseline: NR Followup: NR	Mean change from baseline: -0.8 (SD 2.5), p=NR	Comparator: Standard exercise therapy Difference in mean: p=0.8 SMD: 0.096 (95% CI: - 0.71 to 0.90)	NR	For between group analysis- only p value given
	Arm 2	Qigong	Mean change in dyspnea, baseline to week 6	FACT-G	Final: 6 weeks	Baseline: 11 Followup: 11	Baseline: NR Followup: NR	Mean change from baseline: -0.6 (SD 1.4), p=NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
McMillan, 2007 <sup>15</sup> Behavioral/Psych vs Behavioral/Psych	Arm 2	Standard care and support	Mean change in dyspnea, baseline to 30 days	Dyspnea intensity scale (0-10)	Final: 30 days	Baseline: 109 Followup: 32	Baseline: NR Followup: NR	NR	NR	Group effect, time effect	Random effect model estimates .132 (SE .113)
	Arm 3	Standard care and COPE	Mean change in dyspnea, baseline to 30 days	Dyspnea intensity scale (0-10)	Final: 30 days	Baseline: 111 Followup: 31	Baseline: NR Followup: NR	NR	NR	NR	
Mosher, 2019 <sup>18</sup> Behavioral/Psych vs Behavioral/Psych+ Integrative medicine interventions	Arm 1	Education/ support	Mean change in dyspnea, baseline to 6 weeks	Memorial Symptom Assessment Scale (MSAS)	Final: 6 weeks; Primary: 2 weeks	Baseline: 25 Followup: 18 Primary FU: 18	Baseline: Mean 1.05 (SE 0.19) Followup: Mean 0.69 (SE 0.22) Primary Followup: Mean 0.84 (SE 0.22)	NR	Comparator: Education/ support Difference in mean: p=0.27 SMD: 0.46 (95% CI: -0.10 to 1.02)	Group effect, time effect, role effect	
	Arm 2	Acceptance and Commitment Therapy (ACT)	Mean change in dyspnea, baseline to 6 weeks	Memorial Symptom Assessment Scale (MSAS)	Final: 6 weeks; Primary: 2 weeks	Baseline: 25 Followup: 20 Primary FU: 20	Baseline: Mean 1.08 (SE 0.19) Followup: Mean 1.19 (SE 0.21) Primary Followup: Mean 1.16 (SE 0.21)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Wyatt, 2012 <sup>28</sup> Integrative Medicine Interventions vs Integrative Medicine Interventions	Arm 2	Lay foot manipulation	Mean change in dyspnea	FACT-B scale, dyspnea subscale (0- 4)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 67 Primary FU: 76	Baseline: Mean 2.9 (SD 1.4) Followup: Mean 3 (SD 1.3) Primary Followup: Mean 3 (SD 1.2)	NR	SMD: 0.08 (95% CI: - 0.20 to 0.37)	Baseline anxiety and depression score	
	Arm 3	Reflexology	Mean change in dyspnea	FACT-B scale, dyspnea subscale (0- 4)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 71 Primary FU: 75	Baseline: Mean 3.1 (SD 1.2) Followup: Mean 3.3 (SD 0.9) Primary Followup: Mean 3.3 (SD 1)	NR	NR	NR	
Ramirez, 2018 <sup>22</sup> Placebo vs Integrative Medicine Interventions	Arm 1	Control	Mean change in dyspnea, baseline to 30 minutes,	ESAS	Final: 30 minutes	Baseline: 20 Followup: 20	Baseline: NR Followup: NR	Mean change from baseline: NR, p=NS	NA	NR	
	Arm 2	Music therapy	Mean change in dyspnea, baseline to 30 minutes,	ESAS	Final: 30 minutes	Baseline: 20 Followup: 20	Baseline: NR Followup: NR	Mean change from baseline: NR, p=0.042	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kako, 2018 <sup>13</sup> Placebo vs Respiratory	Arm 1	Fan to legs (control)	Mean change in dyspnea, baseline to 5 minutes,	ESAS-R	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 5.1 (SD 1.52) Followup: NR	Mean change from baseline: -0.1 (SD NR), (95% CI: - 0.53, 0.33), p=NR	Comparator: Control Difference in mean: p<0.001 SMD: -1.16 (95% CI: - 1.83 to -0.49)	NR	
	Arm 2	Fan to face	Mean change in dyspnea, baseline to 5 minutes,	ESAS-R	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 5.3 (SD 1.38) Followup: NR	Mean change from baseline: -1.35 (SD NR), (95% CI: -1.86, -0.84), p=NR	NA	NR	
Ting, 2020 <sup>24</sup> Placebo vs Respiratory	Arm 1	Placebo	Mean change in dyspnea	Modified borg scale (0-10)	Final: 5 minutes	Baseline: 24 Followup: 24	Baseline: NR Followup: NR	Mean change from baseline: -0.15 (SD 0.36), p=NR	Ref	NR	
	Arm 2	Fan on face	Mean change in dyspnea	Modified borg scale (0-10)	Final: 5 minutes	Baseline: 24 Followup: 24	Baseline: NR Followup: NR	Mean change from baseline: -2.79 (SD 0.92), p=NR	Comparator: Arm1 Difference in mean: p<0.0001 SMD: -3.78 (95% CI: - 4.45 to -3.11)	NR	
Vickers, 2005 <sup>26</sup> Placebo vs Integrative medicine interventions	Arm 1	Control	Mean change in dyspnea, baseline to 15 minutes	Dyspnea scale (0-10)	Final: 15 minutes	Baseline: 14 Followup: 14	Baseline: Mean 3.41 (SD 2.79) Followup: Mean 2.42 (SD 2.64)	Mean change from baseline: NR, p=0.003	Comparator: Control Difference in mean : 0.34 (SD NR)(95% CI: -0.33, 1.02), p=0.3 SMD: 0.11 (95% CI: - 0.58 to 0.80)	NR	Worse score in acupuncture group
	Arm 2	Acupuncture/ acupressure	Mean change in dyspnea, baseline to 15 minutes	Dyspnea scale (0-10)	Final: 15 minutes	Baseline: 19 Followup: 19	Baseline: Mean 4.09 (SD 2.32) Followup: Mean 3.36 (SD 2.21)	Mean change from baseline: NR, p=0.003	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Vickers, 2005 <sup>26</sup> Placebo vs Integrative medicine interventions	Arm 1	Control	Mean change in dyspnea, baseline to 7 days	Dyspnea scale (0-10)	Final: 7 days	Baseline: 7 Followup: 14	Baseline: Mean 5.99 (SD 1.71) Followup: Mean 3.77 (SD 2.39)	Mean change from baseline: NR, p=0.07	Comparator: Control Difference in mean : 0.56 (SD NR)(95% CI: -0.39, 1.51), p=0.2 SMD: 0.35 (95% CI: - 0.62 to 1.32)	Group effect, time effect	
	Arm 2	Acupuncture/ acupressure	Mean change in dyspnea, baseline to 7 days	Dyspnea scale (0-10)	Final: 7 days	Baseline: 10 Followup: 16	Baseline: Mean 6.58 (SD 1.71) Followup: Mean 5.07 (SD 2.12)	Mean change from baseline: NR, p=0.4	NA	NR	
Booth, 1996 <sup>1</sup> Respiratory vs Respiratory	Arm 1	Air first	Mean change in dyspnea, baseline to 15 min	VAS (0- 100)	Final: 15 minutes	Baseline: 38 Followup: 38	Baseline: Mean 58.7 (SD 22.7) Followup: Mean 48.7 (SD 14.4)	Mean change from baseline: NR, p<0.001	Comparator: Air p=NS SMD: -0.18 (95% CI: - 0.63 to 0.27)	NR	Baseline and follow-up mean dyspnea score calculated from FIGURE. P value from text
	Arm 2	Standard supplemental oxygen first	Mean change in dyspnea, baseline to 15 min	VAS (0- 100)	Final: 15 minutes	Baseline: 38 Followup: 38	Baseline: Mean 58.7 (SD 22.7) Followup: Mean 44.9 (SD 23)	Mean change from baseline: NR, p<0.001	NA	NR	
Bruera, 1993 <sup>3</sup> Respiratory vs Respiratory	Arm 1	Air first	Mean change in dyspnea (at best), baseline to 5 minutes	VAS (0- 100)	Final: 5 minutes	Baseline: 14 Followup: 14	Baseline: NR Followup: NR	NR	Comparator: Air Difference in mean : 20.5 (SD NR) (95% CI: 13.5, 27.6), p<0.001	Time point, group, stage of cancer	
	Arm 2	Oxygen first	Mean change in dyspnea (at best), baseline to 5 minutes	VAS (0- 100)	Final: 5 minutes	Baseline: 14 Followup: 14	Baseline: NR Followup: NR	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 2003 <sup>4</sup> Respiratory vs Respiratory	Arm 1	Air	Mean dyspnea score after 6- minutes	NRS (0-10)	Final: 6 minutes; Primary: 3 minutes	Baseline: 17 Followup: 17 Primary FU: 17	Baseline: NR Followup: Mean 4.9 (SD 2.7) Primary Followup: Mean 3.8 (SD 2.2)	NR	Comparator: Air p=0.52	NR	Only follow up values and p value for between groups given
	Arm 2	Standard supplemental oxygen	Mean dyspnea score after 6- minutes	NRS (0-10)	Final: 6 minutes; Primary: 3 minutes	Baseline: 16 Followup: 16 Primary FU: 16	Baseline: NR Followup: Mean 4.5 (SD 2.2) Primary Followup: Mean 3.7 (SD 2.1)	NR	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Mean change in dyspnea score (now), baseline and at 2 hours	NRS (0-10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Mean 6.4 (95% CI 5.1, 7.6) Followup: Mean 3.4 (95% CI 1.8- 5.0)	Mean change from baseline: -3.2 (SD NR), (95% CI: -5.1, -1.3), p=0.004	Comparator: High flow oxygen (HFO) Difference in mean: p=0.32 SMD: 0.38 (95% CI: - 0.35 to 1.10)	NR	Between arm comparison of differences in means was limited to p value (.29). In essence, both bilevel ventilation and HFO helped, but one did not help more than other.
	Arm 2	High flow oxygen (HFO)	Mean change in dyspnea score (now), baseline and at 2 hours	NRS (0-10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Mean 5.9 (95% CI 4.5, 7.2) Followup: Mean 4.2 (95% CI 3.1- 5.4)	Mean change from baseline: -1.9 (SD NR), (95% CI: -3.4, -0.4), p=0.02	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Mean change in dyspnea score (now), baseline and at 2 hours	MBS (0-10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Mean 4.4 (95% CI 2.9, 5.8) Followup: Mean 2.6 (95% CI 1.2, 3.9)	Mean change from baseline: -1.5 (SD NR), (95% CI: -3.2, 0.3), p=0.13	Comparator: High flow oxygen (HFO) Difference in mean: p=0.29 SMD: -0.19 (95% CI: - 0.91 to 0.53)	Baseline dyspnea score	Follow-up mean dyspnea scale calculated from FIGURE
	Arm 2	High flow oxygen (HFO)	Mean change in dyspnea score (now), baseline and at 2 hours	MBS (0-10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Mean 4.3 (95% CI 2.5, 6) Followup: Mean 2.5 (95% CI 1.6, 3.3)	Mean change from baseline: -2.1 (SD NR), (95% CI: -3.5, -0.6), p=0.007	NA	NR	Mean difference not given, slope difference is - .58 (-.92, -.23), p .12
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Mean change in dyspnea score, baseline and at 48 hours	Borg scale (0-10)	Final: 48 hours	Baseline: 99 Followup: 88	Baseline: Mean 6.6 (SD 2.1) Followup: Mean 3.6 (95% CI 3.0- 4.1)	NR	Comparator: Oxygen Difference in mean: p=0.0012	Group effect, time effect, interaction	Baseline and follow-up mean dyspnea scale calculated from FIGURE. But differences from table.
	Arm 2	Oxygen	Mean change in dyspnea score, baseline and at 48 hours	Borg scale (0-10)	Final: 48 hours	Baseline: 101 Followup: 101	Baseline: Mean 6.6 (SD 2) Followup: Mean 4.6 (95% CI 4.1- 5.2)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Philip, 2006 <sup>21</sup> Respiratory vs Respiratory	Arm 1	Air first	Median change in dyspnea, baseline to 15 min	VAS (0- 100)	Final: 15 minutes	Baseline: 27 Followup: 27	Baseline: Median 52 (NR), Range: 23-92 Followup: Median 45 (NR), Range: 10, 83	Median change from baseline: -3 (SD NR), (95% CI: -19, 70), p=NR	NA	Carry over, period effects	Both groups improved, but no difference between groups, no AE/ dropout
	Arm 2	Oxygen first	Median change in dyspnea, baseline to 15 min	VAS (0- 100)	Final: 15 minutes	Baseline: 24 Followup: 24	Baseline: Median 43 (NR), Range: 31-78 Followup: Median 34.5 (NR), Range: 0,68	Median change from baseline: -7 (SD NR), (95% CI: -33, 71), p=NR	NA	NR	
Philip, 2006 <sup>21</sup> Respiratory vs Respiratory	Arm 1	Air first	Mean change in dyspnea, baseline to 15 min	VAS (0- 100)	Final: 15 minutes	Baseline: 27 Followup: 27	Baseline: Mean 52 (SE 3.9) Followup: Mean 46.7 (SE 3.2)	Mean change from baseline: 8.7 (SD NR), p=NR	Comparator: Air Difference in mean: p=0.622 SMD: -0.24 (95% CI: - 0.79 to 0.31)	NR	Baseline and follow-up mean dyspnea score calculated from FIGURE. P value from text
	Arm 2	Oxygen first	Mean change in dyspnea, baseline to 15 min	VAS (0- 100)	Final: 15 minutes	Baseline: 24 Followup: 24	Baseline: Mean 48 (SE 2.6) Followup: Mean 38.7 (SE 3.2)	Mean change from baseline: 10.5 (SD NR), p=NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hwang, 2012 <sup>12</sup> Usual care vs Activity/Rehab	Arm 1	Control	Mean change in dyspnea, baseline to 8 weeks	EORTC QLQC30-dyspnea and lung cancer specific symptom QLQ-LC13	Final: 8 weeks	Baseline: 11 Followup: 11	Baseline: Mean 15.2 (SD 14.3) Followup: Mean 13.6 (SD 14.6)	Mean change from baseline: NR, p=0.06	Ref	NR	
	Arm 2	Exercise	Mean change in dyspnea, baseline to 8 weeks	EORTC QLQC30-dyspnea and lung cancer specific symptom QLQ-LC13	Final: 8 weeks	Baseline: 13 Followup: 13	Baseline: Mean 9.6 (SD 10.7) Followup: Mean 3.8 (SD 5.5)	Mean change from baseline: NR, p=0.01	Comparator: Control p=0.06 SMD: -0.35 (95% CI: -1.16 to 0.45)	NR	
Ligibel, 2016 <sup>14</sup> Usual care vs Activity/Rehab	Arm 1	Control	Mean change in dyspnea	EORTC QLQC30	Final: 16 weeks	Baseline: 43 Followup: 43	Baseline: Mean 13.5 (SD 18.1) Followup: NR	Mean change from baseline: 4 (SD 19.8), p=NR	Ref	NR	
	Arm 2	Exercise	Mean change in dyspnea	EORTC QLQC30	Final: 16 weeks	Baseline: 32 Followup: 32	Baseline: Mean 15.6 (SD 18.9) Followup: NR	Mean change from baseline: -6.3 (SD 23.1), p=NR	Comparator: Control p=0.04 SMD: -0.48 (95% CI: -0.95 to -0.02)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Nakano, 2020 <sup>19</sup> Usual care vs Activity/Rehab	Arm 1	Non-TENS	Mean change in dyspnea	EORTC QLQ- C15-PAL	Final: 6 days; Primary:	Baseline: 20 Followup: 20	Baseline: Mean 25 (SD 30.3) Followup: Mean 18.3 (SD 17)	Mean change from baseline: - 6.7 (SD 25.6), p=NR	Ref	NR	
	Arm 2	TENS	Mean change in dyspnea	EORTC QLQ- C15-PAL	Final: 6 days	Baseline: 20 Followup: 20	Baseline: Mean 25 (SD 21.3) Followup: Mean 20 (SD 31.3)	Mean change from baseline: -5 (SD 22.3), p=NR	Comparator: Arm1 Difference in mean : 1.7 (95% CI: -18.7 to 22.2), p=0.87 SMD: 0.07 (95% CI: - 0.55 to 0.69)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Rutkowska, 2019 <sup>23</sup> Usual care vs Activity/Rehab	Arm 1	Control	Mean change in dyspnea	Modified medical research council questionnaire	Final: 6 weeks	Baseline: 10 Followup: 10	Baseline: Mean 0.6 (SD 1) Followup: Mean 0.3 (SD 0.7)	Mean change from baseline: 0.7 (SD 1), p=1	Ref	NR	
	Arm 2	Exercise	Mean change in dyspnea	Modified medical research council questionnaire	Final: 6 weeks	Baseline: 20 Followup: 20	Baseline: Mean 0.7 (SD 0.9) Followup: Mean 0.7 (SD 1)	Mean change from baseline: 0.7 (SD 0.9), p=0.18	Comparator: Control Difference in mean : (NR) p=0.18 SMD: 0 (95% CI: - 0.76 to 0.76)	NR	
Rutkowska, 2019 <sup>23</sup> Usual care vs Activity/Rehab	Arm 1	Control	Mean change in dyspnea	Baseline Dyspnea Index (BDI)	Final: 6 weeks	Baseline: 10 Followup: 10	Baseline: Mean 9.9 (SD 2.6) Followup: Mean 9.8 (SD 2.4)	Mean change from baseline: 9.5 (SD 2.4), p=0.72	Ref	NR	
	Arm 2	Exercise	Mean change in dyspnea	Baseline Dyspnea Index (BDI)	Final: 6 weeks	Baseline: 20 Followup: 20	Baseline: Mean 9.5 (SD 2.1) Followup: Mean 9.5 (SD 2.4)	Mean change from baseline: 9.5 (SD 2.1), p=0.83	Comparator: Control Difference in mean : (NR) p=0.83 SMD: 0 (95% CI: - 0.76 to 0.76)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Rutkowska, 2019 <sup>23</sup> Usual care vs Activity/Rehab	Arm 1	Control	Mean change in dyspnea	Borg score	Final: 6 weeks	Baseline: 10 Followup: 10	Baseline: Mean 1.1 (SD 1) Followup: Mean 2.6 (SD 2.5)	Mean change from baseline: 1.5 (SD 2.1), p=0.42	Ref	NR	
	Arm 2	Exercise	Mean change in dyspnea	Borg score	Final: 6 weeks	Baseline: 20 Followup: 20	Baseline: Mean 1.7 (SD 2.2) Followup: Mean 1.5 (SD 2.1)	Mean change from baseline: 1.7 (SD 2.2), p=0.04	Comparator: Control Difference in mean : (NR) p=0.04 SMD: 0.09 (95% CI: - 0.67 to 0.85)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Chan, 2011 <sup>5</sup> Usual care vs Activity/Rehab +Behavioral/psych	Arm 1	Control	Mean change in dyspnea, baseline to 12 weeks	VAS (0- 100)	Final: 12 weeks; Primary: 6 weeks	Baseline: 70 Followup: 40 Primary FU: 59	Baseline: Mean 20.39 (SD 22.45) Followup: Mean 30.78 (SD 30.24) Primary Followup: Mean 31.36 (SD 25.35)	NR	Comparator : p=0.001	Time point, group, stage of cancer	
	Arm 2	Psychoeducational intervention (PEI)	Mean change in dyspnea, baseline to 12 weeks	VAS (0- 100)	Final: 12 weeks; Primary: 6 weeks	Baseline: 70 Followup: 62 Primary FU: 68	Baseline: Mean 17.11 (SD 17.86) Followup: Mean 19.86 (SD 26.95) Primary Followup: Mean 19.1 (SD 23.11)	NR	Comparator : p=0.001 SMD: -0.30 (95% CI: - 0.63 to 0.03)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Corner, 1996 <sup>6</sup> Usual care vs Activity/Rehab +Behavioral/psych	Arm 1	Control	Median change in dyspnea (at best), baseline to 12 weeks	VAS (0-10)	Final: 12 weeks	Baseline: 9 Followup: 9	Baseline: NR Followup: NR	Median change from baseline: - 0.5 (SD NR), (95% CI: -5.7, 1), p=NR	Comparator: Control Difference in medians: p<0.02	NR	
	Arm 2	Nurse led intervention	Median change in dyspnea (at best), baseline to 12 weeks	VAS (0-10)	Final: 12 weeks	Baseline: 11 Followup: 11	Baseline: NR Followup: NR	Median change from baseline: 0.5 (SD NR), (95% CI: -0.5, 2.8), p=NR	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Dhillon, 2017 <sup>7</sup> Usual care vs Activity/Rehab +Behavioral/psych	Arm 1	Usual care	Mean change in dyspnea	San Diego Shortness of Breath Questionnaire	Final: 6 months; Primary: 2 months	Baseline: 55 Followup: 27 Primary FU: 42	Baseline: Mean 20.56 (NR) Followup: Mean 25.21 (NR) Primary Followup: Mean 22.7 (NR)	NR	Ref	NR	
	Arm 2	Exercise	Mean change in dyspnea	San Diego Shortness of Breath Questionnaire	Final: 6 months; Primary: 2 months	Baseline: 56 Followup: 35 Primary FU: 48	Baseline: Mean 25.25 (NR) Followup: Mean 26.41 (NR) Primary Followup: Mean 27.77 (NR)	NR	Comparator: Arm1 Difference in mean : At 2 months: 5.07 (95% CI: -4.18 to 14.31), p=0.281	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Farquhar, 2014 <sup>9</sup> Usual care vs Activity/Rehab +Behavioral/psych+ Integrative medicine interventions	Arm 1	Control	Mean change in NRS distress due to dyspnea, baseline to 2 weeks	Distress due to dyspnea, NRS 0-10	Final: 2 weeks	Baseline: 26 Followup: 26	Baseline: Mean 4.65 (SD 2.99) Followup: Mean 4.42 (SD 3.01)	Mean change from baseline: 0.23 (SD NR), p=NR	Comparator: Intervention Difference in mean : -1.29 (SD NR) (95% CI: -2.57, - 0.005), p=0.049 SMD: -0.49 (95% CI: -1.04 to 0.05)	Baseline value	
	Arm 2	Intervention	Mean change in NRS distress due to dyspnea, baseline to 2 weeks	Distress due to dyspnea, NRS 0-10	Final: 2 weeks	Baseline: 28 Followup: 28	Baseline: Mean 5.11 (SD 2.78) Followup: Mean 3.43 (SD 2.95)	Mean change from baseline: 1.68 (SD NR), p=NR	NR	NR	
Yorke, 2015 <sup>29</sup> Usual care vs Activity/Rehab +Behavioral/psych+ Integrative medicine interventions	Arm 1	Usual care	Mean change in average dyspnea score, baseline and 12 weeks	NRS (0-10)	Final: 12 weeks	Baseline: 51 Followup: 40	Baseline: Mean 6 (95% CI 5.4, 6.7) Followup: Mean 5 (95% CI 4.3, 5.8)	Mean change from baseline: - 0.75 (SD 2.33), p=NR	Comparator: Respiratory Distress Symptom Intervention (RDSI) Difference in mean : 0.65 (SD 0.58) (95% CI: -0.49, 1.80), p=0.26 SMD: 0.27 (95% CI: -0.12 to 0.66)	NR	Baseline and follow- up mean dyspnea scale calculated from FIGURE. But differences from table.
	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	Mean change in average dyspnea score, baseline and 12 weeks	NRS (0-10)	Final: 12 weeks	Baseline: 50 Followup: 31	Baseline: Mean 4.7 (95% CI 4.1, 5.2) Followup: Mean 4.3 (95% CI 3.4, 5.2)	Mean change from baseline: - 0.17 (SD 2), p=NR	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Yorke, 2015 <sup>29</sup> Usual care vs Activity/Rehab +Behavioral/psych+ Integrative medicine interventions	Arm 1	Usual care	Mean change in average dyspnea score, baseline and 4 weeks	NRS (0-10)	Final: 4 weeks	Baseline: 51 Followup: 41	Baseline: Mean 6 (95% CI 5.4, 6.7) Followup: Mean 5.1 (95% CI 4.4, 5.9)	Mean change from baseline: - 0.38 (SD 2.21), p=NR	Comparator: Respiratory Distress Symptom Intervention (RDSI) Difference in mean : 0.64 (SD 0.5) (95% CI: -0.34, 1.61), p=0.2 SMD: 0.17 (95% CI: -0.22 to 0.56)	NR	
	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	Mean change in average dyspnea score, baseline and 4 weeks	NRS (0-10)	Final: 4 weeks	Baseline: 50 Followup: 31	Baseline: Mean 4.7 (95% CI 4.1, 5.2) Followup: Mean 4.4 (95% CI 3.6, 5.3)	Mean change from baseline: - 0.06 (SD 1.55), p=NR	NR	NR	
Yorke, 2015 <sup>29</sup> Usual care vs Activity/Rehab +Behavioral/psych+ Integrative medicine interventions	Arm 1	Usual care	Mean change in Dyspnea- 12 score, baseline and 12 weeks	Dyspnea-12 (0-36)	Final: 12 weeks	Baseline: 51 Followup: 40	Baseline: Mean 19 (95% CI 16.4, 22.1) Followup: Mean 17.1 (95% CI 13.7, 19.6)	Mean change from baseline: - 1.52 (SD 8.31), p=NR	Comparator: Respiratory Distress Symptom Intervention (RDSI) Difference in mean : 5.19 (SD 2.33) (95% CI: 0.62, 9.75), p=0.026 SMD: -0.19 (95% CI: -0.58 to 0.20)	Group effect, time effect, interaction	
	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	Mean change in Dyspnea- 12 score, baseline and 12 weeks	Dyspnea-12 (0-36)	Final: 12 weeks	Baseline: 50 Followup: 31	Baseline: Mean 16.2 (95% CI 14, 15.8) Followup: Mean 12.2 (95% CI 9.1, 15.2)	Mean change from baseline: - 3.04 (SD 7.78), p=NR	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bordeleau, 2003 <sup>2</sup> Usual care vs Behavioral/psych	Arm 1	Control	Mean change in dyspnea, baseline to 12 months	EORTC QLQ- C-30	Final: 12 months; Primary: 4 months	Baseline: 70 Followup: 18 Primary FU: 36	Baseline: Mean 25.6 (SD 23) Followup: Mean 33.3 (SD 27.2) Primary Followup: Mean 26.9 (SD 23.7)	NR	Ref	Group effect, time effect	
	Arm 2	Intervention	Mean change in dyspnea, baseline to 12 months	EORTC QLQ- C-30	Final: 12 months; Primary: 4 months	Baseline: 145 Followup: 53 Primary FU: 80	Baseline: Mean 29.2 (SD 28) Followup: Mean 36.4 (SD 33.2) Primary Followup: Mean 31.6 (SD 29.3)	NR	Comparator: Control Difference in mean: p=0.96 SMD: -0.02 (95% CI: -0.30 to 0.27)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Moore, 2002 <sup>17</sup> Usual care vs Behavioral/psych	Arm 1	Control	Mean change in dyspnea, baseline to 3 months	EORTC core questionnaire + lung cancer module	Final: 12 months; Primary: 3 months	Baseline: 103 Followup: 29 Primary FU: 74	Baseline: Median 25 (IQR 16.7-50.0) Followup: Median 50 (IQR 20.8-58.3) Primary Followup: Median 33.3 (IQR 25-58.3)	NR	Comparator: Control Difference in medians: p=0.03	NR	
	Arm 2	Nurse-led intervention	Mean change in dyspnea, baseline to 3 months	EORTC core questionnaire + lung cancer module	Final: 12 months; Primary: 3 months	Baseline: 99 Followup: 26 Primary FU: 76	Baseline: Median 25 (IQR 16.7-41.7) Followup: Median 25 (IQR 14.6-50.0) Primary Followup: Median 25 (IQR 16.7-41.7)	NR	NR	NR	
McMillan, 2007 <sup>15</sup> Usual care vs Behavioral/psych	Arm 1	Standard care	Mean change in dyspnea, baseline to 30 days	Dyspnea intensity scale (0-10)	Final: 30 days	Baseline: 109 Followup: 40	Baseline: NR Followup: NR	NR	Comparator: p=0.771	NR	
	Arm 3	Standard care and COPE	Mean change in dyspnea, baseline to 30 days	Dyspnea intensity scale (0-10)	Final: 30 days	Baseline: 111 Followup: 31	Baseline: NR Followup: NR	NR	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
McMillan, 2007 <sup>15</sup> Usual care vs Behavioral/psych	Arm 1	Standard care	Mean change in dyspnea, baseline to 30 days	Dyspnea intensity scale (0-10)	Final: 30 days	Baseline: 109 Followup: 40	Baseline: NR Followup: NR	NR	Comparator: p=0.771	NR	
	Arm 2	Standard care and support	Mean change in dyspnea, baseline to 30 days	Dyspnea intensity scale (0-10)	Final: 30 days	Baseline: 109 Followup: 32	Baseline: NR Followup: NR	NR	NR	Group effect, time effect	Random effect model estimate .132 (SE .113)
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	Median change in MBS, baseline to 4 weeks, BEFORE 6MWT	MBS (0-10)	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Median 4 (IQR 4 to 5) Followup: Median 5 (IQR 5 to 6)	Median change from baseline: NRp≤0.001	Comparator: Control Difference in medians: NR p=0.004	NR	
	Arm 2	Acupressure	Median change in MBS, baseline to 4 weeks, BEFORE 6MWT	MBS (0-10)	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Median 5 (IQR 4 to 6) Followup: Median 2 (IQR 2 to 3)	Median change from baseline: NRp≤0.001	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	Median change in MBS, baseline to 4 weeks, AFTER 6MWT	MBS (0-10)	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Median 6 (IQR 6 to 7) Followup: Median 8 (IQR 7 to 8)	Median change from baseline: NRp≤0.001	Comparator: Control Difference in medians: NR p=0.018	NR	
	Arm 2	Acupressure	Median change in MBS, baseline to 4 weeks, AFTER 6MWT	MBS (0-10)	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Median 8 (IQR 6 to 9) Followup: Median 5 (IQR 3 to 5)	Median change from baseline: NRp≤0.001	NR	NR	
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	Mean change in dyspnea	FACT-B scale, dyspnea subscale (0- 4)	Final: 11 weeks; Primary: 5 weeks	Baseline: 96 Followup: 63 Primary FU: 71	Baseline: Mean 3.1 (SD 1.2) Followup: Mean 2.9 (SD 1.1) Primary Followup: Mean 3 (SD 1)	NR	NR	NR	
	Arm 3	Reflexology	Mean change in dyspnea	FACT-B scale, dyspnea subscale (0- 4)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 71 Primary FU: 75	Baseline: Mean 3.1 (SD 1.2) Followup: Mean 3.3 (SD 0.9) Primary Followup: Mean 3.3 (SD 1)	NR	SMD: 0.36 (95% CI: 0.07 to 0.64)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	Mean change in dyspnea	FACT-B scale, dyspnea subscale (0- 4)	Final: 11 weeks; Primary: 5 weeks	Baseline: 96 Followup: 63 Primary FU: 71	Baseline: Mean 3.1 (SD 1.2) Followup: Mean 2.9 (SD 1.1) Primary Followup: Mean 3 (SD 1)	NR	NR	NR	
	Arm 2	Lay foot manipulation	Mean change in dyspnea	FACT-B scale, dyspnea subscale (0- 4)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 67 Primary FU: 76	Baseline: Mean 2.9 (SD 1.4) Followup: Mean 3 (SD 1.3) Primary Followup: Mean 3 (SD 1.2)	NR	SMD: 0.24 (95% CI: -0.05 to 0.52)	Baseline anxiety and depressio n score	

ACT= Acceptance and Commitment Therapy; AE=adverse events; CI=confidence interval; EORTC QLQ-C30= European Organization for Research and Treatment Quality of Life Questionnaire; ESAS-R= Edmonton Symptom Assessment Scale Revised; FU=follow-up; HFO=high flow oxygen; MBS= Modified Borg Dyspnea Scale; MSAS= Memorial Symptom Assessment Scale; N=sample size; NIV= Noninvasive ventilation; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; RCT=randomized clinical trial; SE=standard error; SMD=standardized mean difference; VAS=Visual Analog Scale



**Evidence Table D-18. Breathlessness categorical outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kako, 2018 <sup>13</sup> Placebo vs Respiratory	Arm 1	Fan to legs (control)	% with 1 point reduction in dyspnea	ESAS-R	Final: 5 minutes	Followup: 20	Final FU: 5/20 (25)	NR	Comparator: p=0.001 RR: 3.2 (95% CI: 1.45 to 7.05)	NR	
	Arm 2	Fan to face	% with 1 point reduction in dyspnea	ESAS-R	Final: 5 minutes	Followup: 20	Final FU: 16/20 (80)	NR	NA	NR	
Kako, 2018 <sup>13</sup> Placebo vs Respiratory	Arm 1	Fan to legs (control)	% with 2 point reduction in dyspnea	ESAS-R	Final: 5 minutes	Followup: 20	Final FU: 1/20 (5)	NR	Comparator: p=0.043 RR: 7.0 (95% CI: 0.95 to 51.8)	NR	
	Arm 2	Fan to face	% with 2 point reduction in dyspnea	ESAS-R	Final: 5 minutes	Followup: 20	Final FU: 7/20 (35)	NR	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Is your dyspnea better	Global Symptom Evaluation (Yes/ no)	Final: 2 hours	Followup: 10	Final FU: 9/10 (90)	NR	NR RR: 0.85 (95% CI: 0.59 to 1.23)	NR	
	Arm 2	High flow oxygen (HFO)	Is your dyspnea better	Global Symptom Evaluation (Yes/ no)	Final: 2 hours	Followup: 13	Final FU: 10/13 (77)	NR	NA	NR	
Philip, 2006 <sup>21</sup> Respiratory vs Respiratory	Arm 1	Air first	% with subjective dyspnea (quite a bit, or very much)	EORTC QLQ-C30 dyspnea measurement	Final: 15 minutes	Followup: 27	Final FU: 7/27 (26)	NR	NR RR: 0.8 (95% CI: 0.29 to 2.2)	NR	
	Arm 2	Oxygen first	% with subjective dyspnea (quite a bit, or very much)	EORTC QLQ-C30 dyspnea measurement	Final: 15 minutes	Followup: 24	Final FU: 5/24 (21)	NR	NA	NR	

CI=confidence interval; EAS-R= Edmonton Symptom Assessment Scale Revised; EORTC QLQ-C30= European Organization for Research and Treatment Quality of Life Questionnaire; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; RCT=randomized clinical trial; SE=standard error; RR=relative risk



**Evidence Table D-19. Patient reported functional continuous outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Henke, 2014 <sup>10</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Control	Mean change in functional status (physical)	EORTC QLQ-C30	Final: 9 weeks	Baseline: 11 Followup: 11	Baseline: Mean 55.38 (SD 29.86) Followup: Mean 48.2 (SD32.9)	NR	Comparator: Control Difference in mean : p<0.05 SMD: 0.23 (95% CI: -0.53 to 0.98)	NR	
	Arm 2	Intervention	Mean change in functional status (physical)	EORTC QLQ-C30	Final: 9 weeks	Baseline: 18 Followup: 18	Baseline: Mean 75.42 (SD 28.46) Followup: Mean 74.58 (SD21.94)	NR	NA	NR	
Bruera, 2003 <sup>4</sup> Respiratory vs Respiratory	Arm 1	Air	Mean fatigue score after 6- minutes	NRS (0- 10)	Final: 6 minutes	Baseline: 17 Followup: 17	Baseline: NR Followup: Mean 4.1 (SD 2.6)	NR	Comparator: Air p=0.64	NR	Baseline and follow-up mean dyspnea score calculated from FIGURE. P value from text
	Arm 2	Standard supplemental oxygen	Mean fatigue score after 6- minutes	NRS (0- 10)	Final: 6 minutes	Baseline: 16 Followup: 16	Baseline: NR Followup: Mean 3.8 (SD 2.3)	NR	NA	NR	
Hwang, 2012 <sup>12</sup> Usual care vs Activity/Rehab	Arm 1	Control	Mean change in functional status, baseline to 8 weeks	EORTC QLQC30 (physical functionin g)	Final: 8 weeks	Baseline: 11 Followup: 11	Baseline: Mean 90.3 (SD 12.1) Followup: Mean 87.9 (SD 11.9)	Mean change from baseline: NR, p=0.26	Comparator: Control p=0.88 SMD: 0.09 (95% CI: -0.71 to 0.90)	NR	
	Arm 2	Exercise	Mean change in functional status, baseline to 8 weeks	EORTC QLQC30 (physical functionin g)	Final: 8 weeks	Baseline: 13 Followup: 13	Baseline: Mean 93.8 (SD 6.9) Followup: Mean 92.3 (SD 6.6)	Mean change from baseline: NR, p=0.17	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Ligibel, 2016 <sup>14</sup> Usual care vs Activity/Rehab	Arm 1	Control	Mean change in functional status	EORTC QLQC30	Final: 16 weeks	Baseline: 43 Followup: 43	Baseline: Mean 85.1 (SD 12.3) Followup: NR	Mean change from baseline: 0.74 (SD ), p=NR	Ref	Race; ethnicity; Eastern Cooperative Oncology Group performance status; menopausal status; presence of visceral metastatic disease; stratification variables; chemotherapy, hormonal therapy, and biologic therapy recorded at baseline; years since the diagnosis of metastatic disease; age; baseline FACIT- Breast Cancer; and baseline Hospital Anxiety and Depression Scale	Extracted adjusted propensity score



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Ligibel, 2016 <sup>14</sup> Usual care vs Activity/Rehab (continued)	Arm 2	Exercise	Mean change in functional status	EORTC QLQC30	Final: 16 weeks	Baseline: 32 Followup: 32	Baseline: Mean 84 (SD 14.3) Followup: NR	Mean change from baseline: 4.47 (SD ), p=NR	Comparator: Control Difference in mean : 3.25 (95% CI: -2.7 to 10.2), p=0.25	race; ethnicity; Eastern Cooperative Oncology Group performance status; menopausal status; presence of visceral metastatic disease; stratification variables; chemotherapy, hormonal therapy, and biologic therapy recorded at baseline; years since the diagnosis of metastatic disease; age; baseline FACIT- Breast Cancer; and baseline Hospital Anxiety and Depression Scale	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Nakano, 2020 <sup>19</sup> Usual care vs Activity/Rehab	Arm 1	Non TENS	Mean change in functional status	EORTC QLQ-C15- PAL	Final: 6 days	Baseline: 20 Followup: 20	Baseline: Mean 60.3 (SD 31.8) Followup: Mean 58.7 (SD 30.2)	Mean change from baseline: - 1.7 (SD 14.7), p=NR	Ref	NR	
	Arm 2	TENS	Mean change in functional status	EORTC QLQ-C15- PAL	Final: 6 days	Baseline: 20 Followup: 20	Baseline: Mean 61.3 (SD 26.6) Followup: Mean 68.6 (SD 26.7)	Mean change from baseline: 7.3 (SD 18.5), p=NR	Comparator: Arm1 Difference in mean : 9 (95% CI: -1.8 to 19.7), p=0.1 SMD: 0.54 (95% CI: -0.09 to 1.17)	NR	
Chan, 2011 <sup>5</sup> Usual care vs Activity/Rehab+ Behavioral/Psych	Arm 1	Control	Mean change in functional status, baseline to 12 weeks	SF-36 (0- 100)	Final: 12 weeks; Primary: 6 weeks	Baseline: 70 Followup: 40 Primary FU: 59	Baseline: Mean 53.01 (SD 27.08) Followup: Mean 53.49 (SD 33.05) Primary Followup: Mean 44.17 (SD 30.44)	NR	Comparator: p=0.034 SMD: 0.18 (95% CI: -0.15 to 0.52)	NR	
	Arm 2	Psychoeducat ional intervention (PEI)	Mean change in functional status, baseline to 12 weeks	SF-36 (0- 100)	Final: 12 weeks; Primary: 6 weeks	Baseline: 70 Followup: 62 Primary FU: 68	Baseline: Mean 50.33 (SD 27.15) Followup: Mean 56.35 (SD 31.45) Primary Followup: Mean 57.51 (SD 27.7)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Corner, 1996 <sup>6</sup> Usual care vs Activity/Rehab+ Behavioral/Psych	Arm 1	Control	Median change in "ADL difficulties", baseline to 12 weeks	Functional Capacity Scale	Final: 12 weeks	Baseline: 9 Followup: 9	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), (95% CI: -3, 2), p=NR	Comparator: Control Difference in medians: p<0.03	NR	
	Arm 2	Nurse led intervention	Median change in "ADL difficulties", baseline to 12 weeks	Functional Capacity Scale	Final: 12 weeks	Baseline: 11 Followup: 11	Baseline: NR Followup: NR	Median change from baseline: 3 (SD NR), (95% CI: -3, 8), p=NR	NA	NR	
Dhillon, 2017 <sup>7</sup> Usual care vs Activity/Rehab+ Behavioral/Psych	Arm 1	Usual care	Mean change in functional status	EORTC QLQ-C30	Final: 6 months; Primary: 2 months	Baseline: 55 Followup: 27 Primary FU: 42	Baseline: Mean 77.38 (NR) Followup: Mean 73.07 (NR) Primary Followup: Mean 77.3 (NR)	NR	Ref	NR	
	Arm 2	Exercise	Mean change in functional status	EORTC QLQ-C30	Final: 6 months; Primary: 2 months	Baseline: 56 Followup: 35 Primary FU: 48	Baseline: Mean 75.85 (NR) Followup: Mean 76.67 (NR) Primary Followup: Mean 78.31 (NR)	NR	Comparator: Arm1 Difference in mean : At 2 months: 1 (95% CI: -7.31 to 9.32), p=0.812	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bordeleau, 2003 <sup>2</sup> Usual care vs Behavioral/Psych	Arm 1	Control	Mean change in functional status (physical), baseline to 12 months	EORTC QLQ-C-30	Final: 12 months; Primary: 4 months	Baseline: 70 Followup: 18 Primary FU: 36	Baseline: Mean 68.9 (SD 23) Followup: Mean 65.8 (SD 21.4) Primary Followup: Mean 66.8 (SD 21.1)	NR	Comparator: Control Difference in mean: p=0.83 SMD: -0.22 (95% CI: -0.51 to 0.07)	Group effect, time effect	
	Arm 2	Intervention	Mean change in functional status (physical), baseline to 12 months	EORTC QLQ-C-30	Final: 12 months; Primary: 4 months	Baseline: 145 Followup: 53 Primary FU: 80	Baseline: Mean 69.1 (SD 22.3) Followup: Mean 60.8 (SD 25.9) Primary Followup: Mean 62.9 (SD 26.3)	NR	NA	NR	
Moore, 2002 <sup>17</sup> Usual care vs Behavioral/Psych	Arm 1	Control	Mean change in physical function, baseline to 3 months	EORTC core questionnaire + lung cancer module	Final: 12 months; Primary: 3 months	Baseline: 103 Followup: 29 Primary FU: 74	Baseline: Median 86.7 (IQR 86.7-93.3) Followup: Median 86.7 (IQR 83.3-93.3) Primary Followup: Median 86.7 (IQR 86.7- 93.3)	NR	Comparator: Control Difference in medians: p=0.22	NR	
	Arm 2	Nurse-led intervention	Mean change in physical function, baseline to 3 months	EORTC core questionnaire + lung cancer module	Final: 12 months; Primary: 3 months	Baseline: 99 Followup: 26 Primary FU: 76	Baseline: Median 86.7 (IQR 86.7-93.3) Followup: Median 86.7 (IQR 80-93.3) Primary Followup: Median 86.7 (IQR 86.7- 93.3)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Wyatt, 2012 <sup>28</sup> Integrative Medicine Interventions vs Integrative Medicine Interventions	Arm 2	Lay foot manipulation	Mean change in functional status, baseline to 11 weeks	SF-36 (0- 100)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 67 Primary FU: 76	Baseline: Mean 58 (SD 26.4) Followup: Mean 62.7 (SD 28.5) Primary Followup: Mean 61.8 (SD 26.8)	NR	SMD: -0.06 (95% CI: -0.35 to 0.22)	Baseline anxiety and depression score	
	Arm 3	Reflexology	Mean change in functional status, baseline to 11 weeks	SF-36 (0- 100)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 71 Primary FU: 75	Baseline: Mean 55.8 (SD 27) Followup: Mean 58.8 (SD 26.4) Primary Followup: Mean 58.1 (SD 27)	NR	NA	NR	
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative Medicine Interventions	Arm 1	Control	Mean change in functional status, baseline to 11 weeks	SF-36 (0- 100)	Final: 11 weeks; Primary: 5 weeks	Baseline: 96 Followup: 63 Primary FU: 71	Baseline: Mean 55.4 (SD 28.3) Followup: Mean 51.9 (SD 26.5) Primary Followup: Mean 53.8 (SD 27.1)	NR	SMD: 0.24 (95% CI: -0.04 to 0.52)	NR	
	Arm 3	Reflexology	Mean change in functional status, baseline to 11 weeks	SF-36 (0- 100)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 71 Primary FU: 75	Baseline: Mean 55.8 (SD 27) Followup: Mean 58.8 (SD 26.4) Primary Followup: Mean 58.1 (SD 27)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative Medicine Interventions	Arm 1	Control	Mean change in functional status, baseline to 11 weeks	SF-36 (0- 100)	Final: 11 weeks; Primary: 5 weeks	Baseline: 96 Followup: 63 Primary FU: 71	Baseline: Mean 55.4 (SD 28.3) Followup: Mean 51.9 (SD 26.5) Primary Followup: Mean 53.8 (SD 27.1)	NR	SMD: 0.30 (95% CI: 0.01 to 0.58)	NR	
	Arm 2	Lay foot manipulation	Mean change in functional status, baseline to 11 weeks	SF-36 (0- 100)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 67 Primary FU: 76	Baseline: Mean 58 (SD 26.4) Followup: Mean 62.7 (SD 28.5) Primary Followup: Mean 61.8 (SD 26.8)	NR	NA	Baseline anxiety and depression score	

Activity/Rehab=activity and rehabilitation intervention; ADL=activities of daily living; Behavioral/Psych=behavioral and psychoeducational intervention; CI=confidence interval; EORTC QLQ-C30= European Organization for Research and Treatment Quality of Life Questionnaire; FU=follow-up; N=sample size; NR=not reported; NRS=numerical rating scale; NS=non-significant; p=p-value; RCT=randomized clinical trial; SD=standard deviation; SE=standard error; SF-36= 36-Item Short Form Survey; SMD=standardized mean difference



Evidence Table D-20. Quality of life continuous outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients

	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Activity/Rehab vs Activity/Rehab	Henke, 2014 <sup>10</sup>	Arm 1	Control	Mean change in global QOL	EORTC QLQ-C30	Final: 9 weeks	Baseline: 11 Followup: 11	Baseline: Mean 50.64 (SD 28.15) Followup: Mean 44.23 (SD29.54)	NR	Comparator: Control Difference in mean : p>0.05 SMD: 0.51 (95% CI: -0.25 to 1.28)	NR	
	Henke, 2014 <sup>10</sup>	Arm 2	Intervention	Mean change in global QOL	EORTC QLQ-C30	Final: 9 weeks	Baseline: 18 Followup: 18	Baseline: Mean 52.08 (SD 21.84) Followup: Mean 57.81 (SD17.34)	NR	NA	NR	
	Vanderbyl, 2017 <sup>25</sup>	Arm 1	Standard exercise therapy	Mean change in QOL, baseline to week 6	FACT-G	Final: 6 weeks	Baseline: 13 Followup: 13	Baseline: Mean 73.6 (SD 14.5) Followup: NR	Mean change from baseline: 3.5 (SD 14.1), p=NR	Comparator: Standard exercise therapy Difference in mean: p=0.98 SMD: 0.01 (95% CI: -0.79 to 0.81)	NR	Baseline and follow-up mean dyspnea scores calculated from FIGURE. Both differences were not significant in the difference from table.
	Vanderbyl, 2017 <sup>25</sup>	Arm 2	Qigong	Mean change in QOL, baseline to week 6	FACT-G	Final: 6 weeks	Baseline: 11 Followup: 11	Baseline: Mean 70.2 (SD 14.6) Followup: NR	Mean change from baseline: 3.6 (SD 6.6), p=NR	NA	NR	



	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Usual care vs Activity/Rehab	Hwang, 2012 <sup>12</sup>	Arm 1	Control	Mean change in QOL, baseline to 8 weeks	EORTC QLQC30 (global health status and QOL)	Final: 8 weeks	Baseline: 11 Followup: 11	Baseline: Mean 62.1 (SD 14.1) Followup: Mean 65.2 (SD 15.3)	Mean change from baseline: NR, p=0.34	Comparator: Control p=0.45 SMD: 0.13 (95% CI: -0.67 to 0.94)	Baseline value	
	Hwang, 2012 <sup>12</sup>	Arm 2	Exercise	Mean change in QOL, baseline to 8 weeks	EORTC QLQC30 (global health status and QOL)	Final: 8 weeks	Baseline: 13 Followup: 13	Baseline: Mean 73.1 (SD 14.5) Followup: Mean 78.2 (SD 16.1)	Mean change from baseline: NR, p=0.017	NA	NR	
	Ligibel, 2016 <sup>14</sup>	Arm 1	Control	Mean change in QOL	EORTC QLQC30	Final: 16 weeks	Baseline: 43 Followup: 43	Baseline: Mean 71.5 (SD 20.2) Followup: NR	Mean change from baseline: -1 (SD 21.5), p=NR	Ref	NR	
	Ligibel, 2016 <sup>14</sup>	Arm 2	Exercise	Mean change in QOL	EORTC QLQC30	Final: 16 weeks	Baseline: 32 Followup: 32	Baseline: Mean 67.2 (SD 19.4) Followup: NR	Mean change from baseline: 6 (SD 17.5), p=NR	Comparator: Control Difference in mean : (NR) p=0.17 SMD: 0.35 (95% CI: -0.11 to 0.81)	NR	



	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Usual care vs Activity/Rehab+ Behavioral/Psych	Dhillon, 2017 <sup>7</sup>	Arm 1	Usual care	Mean change in QOL	EORTC QLQ-C30	Final: 6 months; Primary: 2 months	Baseline: 55 Followup: 27 Primary FU: 42	Baseline: Mean 58.92 (NR) Followup: Mean 54.42 (NR) Primary Followup: Mean 64.26 (NR)	NR	Ref	NR	
	Dhillon, 2017 <sup>7</sup>	Arm 2	Exercise	Mean change in QOL	EORTC QLQ-C30	Final: 6 months; Primary: 2 months	Baseline: 56 Followup: 35 Primary FU: 48	Baseline: Mean 63.84 (NR) Followup: Mean 61.21 (NR) Primary Followup: Mean 63.15 (NR)	NR	Comparator: Arm1 Difference in mean : At 2 months: -1.12 (95% CI: -10.6 to 8.37), p=0.817	NR	
Usual care vs Activity/Rehab+ Behavioral/Psych+ Integrative medicine interventions	Farquhar, 2014 <sup>9</sup>	Arm 1	Control	Mean change in QOL, baseline to 2 weeks	Chronic respiratory questionn aire (CRQ)- 7	Final: 2 weeks	Baseline: 26 Followup: 26	Baseline: Mean 4.71 (SD 1.27) Followup: Mean 4.72 (SD 1.21)	NR	Comparator: Intervention Difference in mean : 0.2 (SD NR) (95% CI: - 0.35, 0.76), p=0.47 SMD: 0.22 (95% CI: -0.32 to 0.76)	Baseline anxiety and depressi on score	Participants reflexology reported statistically significant reductions dyspnea se compared t control grou .1) and the group (p =. adjusted ef sizes for reflexology control wer week 5 and week 11 fo dyspnea



	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Usual care vs Activity/Rehab+ Behavioral/Psych+ Integrative medicine interventions	Farquhar, 2014 <sup>9</sup>	Arm 2	Intervention	Mean change in QOL, baseline to 2 weeks	Chronic respiratory questionn aire (CRQ)- 7	Final: 2 weeks	Baseline: 28 Followup: 28	Baseline: Mean 4.53 (SD 1.13) Followup: Mean 4.81 (SD 1.29)	NR	NA	NR	
	Yorke, 2015 <sup>29</sup>	Arm 1	Usual care	Mean change in QOL, baseline to week 12	EQ-5D-3L score	Final: 12 weeks	Baseline: 51 Followup: 40	Baseline: NR Followup: NR	Mean change from baseline: - 0.05 (SD 0.33), p=NR	Comparator: Respiratory Distress Symptom Intervention (RDSI) Difference in mean : -0.17 (SD 0.65) (95% CI: - 0.30, -0.04), p=0.009 SMD: 0.36 (95% CI: -0.03 to 0.75)	NR	For between analysis- or value given
	Yorke, 2015 <sup>29</sup>	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	Mean change in QOL, baseline to week 12	EQ-5D-3L score	Final: 12 weeks	Baseline: 50 Followup: 31	Baseline: NR Followup: NR	Mean change from baseline: 0.06 (SD 0.28), p=NR	NA	NR	



	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Usual care vs Behavioral/Psych	Bordeleau, 2003 <sup>2</sup>	Arm 1	Control	Mean change in global QOL, baseline to 12 months	EORTC QLQ-C-30	Final: 12 months; Primary: 4 months	Baseline: 70 Followup: 18 Primary FU: 36	Baseline: Mean 64.5 (SD 18.4) Followup: Mean 58.8 (SD 23.5) Primary Followup: Mean 61.6 (SD 21.4)	NR	Comparator: Control Difference in mean: p=0.84 SMD: 0.15 (95% CI: -0.13 to 0.44)	Group effect, time effect	Random ef model estim (SE .11)
	Bordeleau, 2003 <sup>2</sup>	Arm 2	Intervention	Mean change in global QOL, baseline to 12 months	EORTC QLQ-C-30	Final: 12 months; Primary: 4 months	Baseline: 145 Followup: 53 Primary FU: 80	Baseline: Mean 62.2 (SD 21.1) Followup: Mean 59.7 (SD 20.2) Primary Followup: Mean 59.2 (SD 20.7)	NR	NA	NR	
	Moore, 2002 <sup>17</sup>	Arm 1	Control	Mean change in global QOL, baseline to 3 months	EORTC core questionn aire + lung cancer module	Final: 12 months; Primary: 3 months	Baseline: 103 Followup: 29 Primary FU: 74	Baseline: Median 58.3 (IQR 50.0- 68.8) Followup: Median 58.3 (IQR 41.7- 75.0) Primary Followup: Median 66.7 (IQR 50.0- 83.3)	NR	Comparator: Control Difference in medians: p=0.82	NR	Worse scor acupunctur
	Moore, 2002 <sup>17</sup>	Arm 2	Nurse-led intervention	Mean change in global QOL, baseline to 3 months	EORTC core questionn aire + lung cancer module	Final: 12 months; Primary: 3 months	Baseline: 99 Followup: 26 Primary FU: 76	Baseline: Median 66.7 (IQR 50.0- 83.3) Followup: Median 66.7 (IQR 50.0- 75) Primary Followup: Median 66.7 (IQR 50.0- 81.3)	NR	NA	NR	



	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Behavioral/Psych vs Behavioral/Psych	McMillan, 2007 <sup>15</sup>	Arm 2	Standard care and support	Mean change in QOL, baseline to 30 days	Hospice Quality-of- Life Index (HQLI)	Final: 30 days	Baseline: 109 Followup: 32	Baseline: NR Followup: NR	NR	NR	NR	
	McMillan, 2007 <sup>15</sup>	Arm 3	Standard care and COPE	Mean change in QOL, baseline to 30 days	Hospice Quality-of- Life Index (HQLI)	Final: 30 days	Baseline: 111 Followup: 31	Baseline: NR Followup: NR	NR	NR	NR	
Usual care vs Behavioral/Psych	McMillan, 2007 <sup>15</sup>	Arm 1	Standard care	Mean change in QOL, baseline to 30 days	Hospice Quality-of- Life Index (HQLI)	Final: 30 days	Baseline: 109 Followup: 40	Baseline: NR Followup: NR	NR	Comparator: p=0.246	NR	
	McMillan, 2007 <sup>15</sup>	Arm 3	Standard care and COPE	Mean change in QOL, baseline to 30 days	Hospice Quality-of- Life Index (HQLI)	Final: 30 days	Baseline: 111 Followup: 31	Baseline: NR Followup: NR	NR	NA	NR	
	McMillan, 2007 <sup>15</sup>	Arm 1	Standard care	Mean change in QOL, baseline to 30 days	Hospice Quality-of- Life Index (HQLI)	Final: 30 days	Baseline: 109 Followup: 40	Baseline: NR Followup: NR	NR	Comparator: p=0.246	NR	
	McMillan, 2007 <sup>15</sup>	Arm 2	Standard care and support	Mean change in QOL, baseline to 30 days	Hospice Quality-of- Life Index (HQLI)	Final: 30 days	Baseline: 109 Followup: 32	Baseline: NR Followup: NR	NR	NA	NR	



	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
<b>Integrative Medicine Interventions vs Integrative Medicine Interventions</b>	Wyatt, 2012 <sup>28</sup>	Arm 2	Lay foot manipulation	Mean change in QOL, baseline to 11 weeks	FACT-B v4 (0-180)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 67 Primary FU: 76	Baseline: Mean 93.1 (SD 20.6) Followup: Mean 99.7 (SD 21.5) Primary Followup: Mean 98 (SD 19.3)	NR	SMD: -0.04 (95% CI: -0.32 to 0.24)	NR	
	Wyatt, 2012 <sup>28</sup>	Arm 3	Reflexology	Mean change in QOL, baseline to 11 weeks	FACT-B v4 (0-180)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 71 Primary FU: 75	Baseline: Mean 95.3 (SD 19.1) Followup: Mean 101.1 (SD 18.3) Primary Followup: Mean 96 (SD 20.4)	NR	NA	NR	
<b>Usual care vs Integrative Medicine Interventions</b>	Dogan, 2019 <sup>8</sup>	Arm 1	Control	Mean change in QOL, baseline to 4 weeks	St George's Respiratory Questionnaire (0-100)	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Mean 53.83 (SD9.06 ) Followup: Mean 67.83 (SD 9.59)	Mean change from baseline: NR, p≤0.001	Comparator: Control Difference in mean : NR p≤0.001 SMD: -3.94 (95% CI: -4.82 to -3.06)	NR	
	Dogan, 2019 <sup>8</sup>	Arm 2	Acupressure	Mean change in QOL, baseline to 4 weeks	St George's Respiratory Questionnaire (0-100)	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Mean 57.71 (SD7.07 ) Followup: Mean 36.14 (SD 9.71)	Mean change from baseline: NR, p≤0.001	NA	NR	



	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Usual care vs Integrative Medicine Interventions	Wyatt, 2012 <sup>28</sup>	Arm 1	Control	Mean change in QOL, baseline to 11 weeks	FACT-B v4 (0-180)	Final: 11 weeks; Primary: 5 weeks	Baseline: 96 Followup: 63 Primary FU: 71	Baseline: Mean 96.7 (SD 19.4) Followup: Mean 100.4 (SD 18.7) Primary Followup: Mean 99.4 (SD 19)	NR	SMD: -0.10 (95% CI: -0.43 to 0.22)	NR	
	Wyatt, 2012 <sup>28</sup>	Arm 3	Reflexology	Mean change in QOL, baseline to 11 weeks	FACT-B v4 (0-180)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 71 Primary FU: 75	Baseline: Mean 95.3 (SD 19.1) Followup: Mean 101.1 (SD 18.3) Primary Followup: Mean 96 (SD 20.4)	NR	NA	NR	
	Wyatt, 2012 <sup>28</sup>	Arm 1	Control	Mean change in QOL, baseline to 11 weeks	FACT-B v4 (0-180)	Final: 11 weeks; Primary: 5 weeks	Baseline: 96 Followup: 63 Primary FU: 71	Baseline: Mean 96.7 (SD 19.4) Followup: Mean 100.4 (SD 18.7) Primary Followup: Mean 99.4 (SD 19)	NR	SMD: 0.1121893 (95% CI: - 0.2115657 to 0.4359443)	NR	
	Wyatt, 2012 <sup>28</sup>	Arm 2	Lay foot manipulation	Mean change in QOL, baseline to 11 weeks	FACT-B v4 (0-180)	Final: 11 weeks; Primary: 5 weeks	Baseline: 95 Followup: 67 Primary FU: 76	Baseline: Mean 93.1 (SD 20.6) Followup: Mean 99.7 (SD 21.5) Primary Followup: Mean 98 (SD 19.3)	NR	NA	NR	



	Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Usual care vs Respiratory	Molassiotis, 2015 <sup>16</sup>	Arm 1	Control	Mean change in QOL, baseline to week 12	Chronic Respirator y Disease Questionn aire-short form (CRDQ)- FATIGUE	Final: 12 weeks	Baseline: 23 Followup: 18	Baseline: NR Followup: Mean 6.8 (SD 1.9)	NR	NR	NR	Only follow values and for between given
	Molassiotis, 2015 <sup>16</sup>	Arm 2	Inspiratory muscle training (IMT)	Mean change in QOL, baseline to week 12	Chronic Respirator y Disease Questionn aire-short form (CRDQ)- FATIGUE	Final: 12 weeks	Baseline: 24 Followup: 18	Baseline: NR Followup: Mean 8.8 (SD 2.2)	NR	NR	NR	

Activity/Rehab=activity and rehabilitation intervention; ADL=activities of daily living; Behavioral/Psych=behavioral and psychoeducational intervention; CI=confidence interval; CRDQ= Chronic Respiratory Disease Questionnaire-short form; CRQ= Chronic respiratory questionnaire; EORTC QLQ-C30= European Organization for Research and Treatment Quality of Life Questionnaire; 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; FU=follow-up; HQLI= Hospice Quality-of-Life Index; N=sample size; NR=not reported; NRS=numerical rating scale; NS=non-significant; p=p-value; QOL=quality of life; RCT=randomized clinical trial; SD=standard deviation; SE=standard error; SF-36= 36-Item Short Form Survey; SMD=standardized mean difference



**Evidence Table D-21. Blood pressure continuous outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Systolic BP	mm Hg	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Mean 125 (SD 18) Followup: Mean 124 (SD 17)	Mean change from baseline: - 3.4 (SD 14.5), p=0.73	Comparator: High flow oxygen (HFO) Difference in mean: p=0.1 SMD: -0.63 (95% CI: - 1.36 to 0.11)	NR	Between arm comparison of differences in means was limited to p value
	Arm 2	High flow oxygen (HFO)	Systolic BP	mm Hg	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Mean 135 (SD 18) Followup: Mean 122 (SD 16)	Mean change from baseline: - 12.6 (SD 14.8), p=0.02	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Diastolic BP	mm Hg	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Mean 73 (SD 9) Followup: Mean 72 (SD 14)	Mean change from baseline: - 0.2 (SD 7.8), p=0.99	Comparator: High flow oxygen (HFO) Difference in mean: p=0.23 SMD: -0.22 (95% CI: - 0.945 to 0.50)	NR	Only pre data, and mean differences between groups reported
	Arm 2	High flow oxygen (HFO)	Diastolic BP	mm Hg	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Mean 79 (SD 12) Followup: Mean 76 (SD 11)	Mean change from baseline: - 2.1 (SD 9.4), p=0.79	NA	NR	
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Mean BP	mm Hg	Final: 48 hours	Baseline: 99 Followup: 99	Baseline: Mean 86 (SD 14.3) Followup: NR	NR	Comparator: Oxygen Difference in mean: -0.51 (SD NR) (95% CI: -2.13, 1.12), p=NR	NR	For between group analysis- only p value given
	Arm 2	Oxygen	Mean BP	mm Hg	Final: 48 hours	Baseline: 101 Followup: 101	Baseline: Mean 83 (SD 13.7) Followup: NR	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hwang, 2012 <sup>12</sup> Usual care vs Activity/Rehab	Arm 1	Control	Systolic BP	mm Hg	Final: 8 weeks	Baseline: 10 Followup: 10	Baseline: Mean 167 (SD 24) Followup: Mean 169 (SD 21)	NR	Comparator: Control Difference in mean: p=0.33 SMD: 0.43 (95% CI: - 0.44 to 1.30)	Time, group effect	
	Arm 2	Exercise	Systolic BP	mm Hg	Final: 8 weeks	Baseline: 11 Followup: 11	Baseline: Mean 171 (SD 11) Followup: Mean 181 (SD 16)	NR	NA	NR	
Hwang, 2012 <sup>12</sup> Usual care vs Activity/Rehab	Arm 1	Control	Diastolic BP	mm Hg	Final: 8 weeks	Baseline: 10 Followup: 10	Baseline: Mean 72 (SD 6) Followup: Mean 95 (SD 10)	NR	Comparator: Control Difference in mean: p=0.31 SMD: -9.134909 (95% CI: -12.16296 to - 6.106862)	NR	
	Arm 2	Exercise	Diastolic BP	mm Hg	Final: 8 weeks	Baseline: 11 Followup: 11	Baseline: Mean 78 (SD 10) Followup: Mean 15 (SD 10)	NR	NA	NR	

Activity/Rehab=activity and rehabilitation intervention; BP=blood pressure; CI=confidence interval; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RCT=randomized clinical trial; SD=standard deviation; SE=standard error; SMD=standardized mean difference



**Evidence Table D-22. Clinical functional continuous outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Rutkowska, 2019 <sup>23</sup> Usual care vs Activity/Rehab	Arm 1	Control	6-minute walk test	NR	Final: 6 weeks	Baseline: 10 Followup: 10	Baseline: Mean 487 (SD 100) Followup: Mean 490 (SD 124)	Mean change from baseline: (SD ), p=0.92	Ref	NR	Table 2 in article, cannot determine between group effect size, table unclear
	Arm 2	Exercise	6-minute walk test	NR	Final: 6 weeks	Baseline: 20 Followup: 20	Baseline: Mean 486 (SD 92) Followup: Mean 531 (SD 103)	Mean change from baseline: (SD ), p=0.01	Comparator: Control Difference in mean : NR p=0.09 SMD: 0.41 (95% CI: -0.36 to 1.17)	NR	
Dhillon, 2017 <sup>7</sup> Usual care vs Activity/Rehab+ Behavioral/Psych	Arm 1	Usual care	6-minute walk test	0	Final: 6 months; Primary: 2 months	Baseline: 55 Followup: 27 Primary FU: 42	Baseline: Mean 234.9 (NR) Followup: Mean 538 (NR) Primary Followup: Mean 516.3 (NR)	NR	Ref	NR	
	Arm 2	Exercise	6-minute walk test	0	Final: 6 months; Primary: 2 months	Baseline: 56 Followup: 35 Primary FU: 48	Baseline: Mean 251 (NR) Followup: Mean 545.3 (NR) Primary Followup: Mean 517.7 (NR)	NR	Comparator: Arm1 Difference in mean : At 6 months: 1.39 (95% CI: -75.9, 78.64), p=0.972	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 2003 <sup>4</sup> Respiratory vs Respiratory	Arm 1	Air	Mean 6-minute walk test	6-minute walk test (meters)	Final: 6 minutes	Baseline: 17 Followup: 17	Baseline: NR Followup: Mean 1085 (SD 189)	NR	Comparator: Air p=0.95	NR	
	Arm 2	Standard supplemental oxygen	Mean 6-minute walk test	6-minute walk test (meters)	Final: 6 minutes	Baseline: 16 Followup: 16	Baseline: NR Followup: Mean 1088 (SD 180)	NR	NA	NR	

N=sample size; NR=not reported; p=p-value; SD=standard deviation



**Evidence Table D-23. Heart rate continuous outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kako, 2018 <sup>13</sup> Placebo vs Respiratory	Arm 1	Fan to legs (control)	Heart rate	HR/ minute	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 94.3 (SD 17.3) Followup: Mean 92.4 (SD 17.3)	Mean change from baseline: NR, p=0.125	SMD: -0.20 (95% CI: -0.82 to 0.42)	NR	
	Arm 2	Fan to face	Heart rate	HR/ minute	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 93.9 (SD 17.4) Followup: Mean 88 (SD 25.3)	Mean change from baseline: NR, p=0.114	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Heart rate	HR/ minute	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Mean 95.6 (SD 17.4) Followup: Mean 85.4 (SD 10.5)	Mean change from baseline: - 5.0 (SD 5.1), p=0.02	Comparator: High flow oxygen (HFO) Difference in mean: p=0.43 SMD: 0.41 (95% CI: -0.31 to 1.14)	NR	Between arm comparison of differences in means was limited to p value
	Arm 2	High flow oxygen (HFO)	Heart rate	HR/ minute	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Mean 101.2 (SD 17.2) Followup: Mean 97.7 (SD 17.3)	Mean change from baseline: - 3.6 (SD 7.8), p=0.42	NA	NR	
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Heart rate	HR/ minute	Final: 48 hours	Baseline: 99 Followup: 99	Baseline: Mean 101 (SD 18.1) Followup: NR	NR	Comparator: Oxygen Difference in mean: - 3.07 (SD NR) (95% CI: -5.66, -0.48), p=NR	NR	Only pre data, and mean differences between groups reported
	Arm 2	Oxygen	Heart rate	HR/ minute	Final: 48 hours	Baseline: 101 Followup: 101	Baseline: Mean 102 (SD 20.8) Followup: NR	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	HR before 6MWT	NR	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Mean 78.03 (SD 10.49) Followup: Mean 81.87 (SD 8.14)	Mean change from baseline: NR, p=0.024	Comparator: Control p=0.349 SMD: -0.60 (95% CI: -1.12 to -0.08)	NR	
	Arm 2	Acupressure	HR before 6MWT	NR	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Mean 84.14 (SD 13) Followup: Mean 81.72 (SD 8.19)	Mean change from baseline: NR, p=0.322	NA	NR	
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	HR after 6MWT	NR	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Mean 97.67 (SD 7.88) Followup: Mean 99.87 (SD 7.78)	Mean change from baseline: NR, p=0.164	Comparator: Control p=0.245 SMD: -0.68 (95% CI: -1.20 to -0.15)	NR	
	Arm 2	Acupressure	HR after 6MWT	NR	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Mean 99.86 (SD 13.01) Followup: Mean 95.44 (SD 8.97)	Mean change from baseline: NR, p=0.61	NA	NR	
Hwang, 2012 <sup>12</sup> Usual care vs Activity/Rehab	Arm 1	Control	Heart rate	HR/ minute	Final: 8 weeks	Baseline: 10 Followup: 10	Baseline: Mean 127 (SD 11) Followup: Mean 130 (SD 15)	NR	Comparator: Control Difference in mean: p=0.55 SMD: 0.16 (95% CI: -0.66 to 0.99)	Time, group effect	
	Arm 2	Exercise	Heart reate	HR/ minute	Final: 8 weeks	Baseline: 13 Followup: 13	Baseline: Mean 134 (SD 11) Followup: Mean 139 (SD 12)	NR	NA	NR	

6MWT=6 minute walk test; Activity/Rehab=activity and rehabilitation intervention; CI=confidence interval; FU=follow-up; HR=heart rate; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RCT=randomized clinical trial; SD=standard deviation; SE=standard error; SMD=standardized mean difference



**Evidence Table D-24. Hospitalization categorical outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Farquhar, 2014 <sup>9</sup> Usual care vs Activity/Rehab+ Behavioral/Psych+ Integrative medicine interventions	Arm 1	Control	Hospitalizations	NR	Final: 2 weeks	Followup: 26	Final FU: 3/26 (12)	NR	RR: 0.62 (95% CI: 0.11 to 3.41)	NR	
	Arm 2	Intervention	Hospitalizations	NR	Final: 2 weeks	Followup: 28	Final FU: 2/28 (7)	NR	NA	NR	

Activity/Rehab=activity and rehabilitation intervention; Behavioral/Psych=behavioral and psychoeducational intervention; CI=confidence interval; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RCT=randomized clinical trial; RR=relative risk; SD=standard deviation; SE=standard error



**Evidence Table D-25. Objective measures continuous outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Henke, 2014 <sup>10</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Control	6-minute walk test	meters	Final: 9 weeks	Baseline: 11 Followup: 11	Baseline: Mean 240.83 (SD 150.5) Followup: Mean 193.33 (SD 162.78)	Mean change from baseline: NR, p<0.05	Comparator: Control Difference in mean: p<0.05 SMD: 0.52 (95% CI: - 0.245 to 1.29)	NR	
	Arm 2	Intervention	6-minute walk test	meters	Final: 9 weeks	Baseline: 18 Followup: 18	Baseline: Mean 378.35 (SD 106.71) Followup: Mean 397.06 (SD 102.56)	Mean change from baseline: NR, p<0.05	NA	NR	
Vanderbyl, 2017 <sup>25</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Standard exercise therapy	Mean change in 6 minute walk test, baseline to week 6	6-minute walk test (meters)	Final: 6 weeks	Baseline: 13 Followup: 13	Baseline: Mean 420 (SD 85.8) Followup: NR	Mean change from baseline: 73.3 (SD 60.1), p=NR	Comparator: Standard exercise therapy Difference in mean: p=0.002 SMD: -1.43 (95% CI: - 2.334 to -0.52)	NR	Only follow up values and p value for between groups given
	Arm 2	Qigong	Mean change in 6 minute walk test, baseline to week 6	6-minute walk test (meters)	Final: 6 weeks	Baseline: 11 Followup: 11	Baseline: Mean 430.6 (SD 66.2) Followup: NR	Mean change from baseline: - 4 (SD 45.7), p=NR	NA	NR	
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	6-minute walk test	NR	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Median 308 (IQR 276 to 326) Followup: Median 284 (IQR 262 to 306)	Median change from baseline: NR, p=0.004	Comparator: Control p=0.046	NR	
	Arm 2	Acupressure	6-minute walk test	NR	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Median 286 (IQR 262 to 326) Followup: Median 320 (IQR 309 to 365)	Median change from baseline: NR, p≤0.001	NA	NR	

Activity/Rehab=activity and rehabilitation intervention; CI=confidence interval; IQR=interquartile range; N=sample size; NR=not reported; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-26. Oxygen saturation continuous outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kako, 2018 <sup>13</sup> Placebo vs Respiratory	Arm 1	Fan to legs (control)	Oxygen saturation	%	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 96.7 (SD 2) Followup: Mean 96.9 (SD 1.8)	Mean change from baseline: NR, p=0.408	SMD: -0.10 (95% CI: -0.72 to 0.52)	NR	
	Arm 2	Fan to face	Oxygen saturation	%	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 95.7 (SD 2) Followup: Mean 95.7 (SD 2.1)	Mean change from baseline: NR, p=0.858	NA	NR	
Ting, 2020 <sup>24</sup> Placebo vs Respiratory	Arm 1	Placebo	Oxygen saturation	O2 sat %	Final: 5 minutes	Baseline: 24 Followup: 24	Baseline: NR Followup: NR	Mean change from baseline: -0.1 (SD 0.31), p=NR	Ref	NR	
	Arm 2	Fan on face	Oxygen saturation	O2 sat %	Final: 5 minutes	Baseline: 24 Followup: 24	Baseline: NR Followup: NR	Mean change from baseline: -0.67 (SD 0.75), p=NR	Comparator: Arm1 Difference in mean: p<0.0001 SMD: -0.99 (95% CI: -1.42 to -0.57)	NR	
Bruera, 1993 <sup>3</sup> Respiratory vs Respiratory	Arm 1	Air first	Oxygen saturation	%	Final: 5 minutes	Baseline: 7 Followup: 7	Baseline: NR Followup: NR	Mean change from baseline: -0.5 (SD NR), (95% CI: -1.3, 0.3), p=0.23	SMD: -0.99 (95% CI: -2.11 to 0.13)	Time, group effect	
	Arm 2	Oxygen first	Oxygen saturation	%	Final: 5 minutes	Baseline: 7 Followup: 7	Baseline: NR Followup: NR	Mean change from baseline: -9.1 (SD NR), (95% CI: - 10.6, 7.6), p=0	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Oxygen saturation	%	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Mean 98.8 (SD 13.4) Followup: Mean 97.9 (SD 4)	Mean change from baseline: 3.3 (SD 5.3), p=0.11	Comparator: High flow oxygen (HFO) Difference in mean: p=0.62 SMD: 0.38 (95% CI: -0.345 to 1.10)	NR	Between arm comparison of differences in means was limited to p value
	Arm 2	High flow oxygen (HFO)	Oxygen saturation	%	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Mean 93.1 (SD 5.4) Followup: Mean 98.5 (SD 2.1)	Mean change from baseline: 5.3 (SD 5.2), p=0.003	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Transcutaneous Co2	mm Hg	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Mean 35.5 (SD 7.4) Followup: Mean 36.5 (SD 9.2)	Mean change from baseline: 1.9 (SD 2.7), p=0.04	Comparator: High flow oxygen (HFO) Difference in mean: p=0.02 SMD: -0.66 (95% CI: -1.40 to 0.08)	NR	Between arm comparison of differences in means was limited to p value
	Arm 2	High flow oxygen (HFO)	Transcutaneous Co2	mm Hg	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Mean 37.8 (SD 6.3) Followup: Mean 36.9 (SD 9.2)	Mean change from baseline: -0.9 (SD 5.5), p=0.06	NA	NR	
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	PaO2/ Fio2	mm Hg	Final: 48 hours	Baseline: 99 Followup: 99	Baseline: Mean 185 (SD 74) Followup: NR	NR	Comparator: Oxygen Difference in mean: 5.17 (SD NR) (95% CI: 1.98, 8.35), p=NR	NR	Only pre data, and mean differences between groups reported
	Arm 2	Oxygen	PaO2/ Fio2	mm Hg	Final: 48 hours	Baseline: 101 Followup: 101	Baseline: Mean 183 (SD 62) Followup: NR	NR	NA	NR	
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	PaCo2	mm Hg	Final: 48 hours	Baseline: 99 Followup: 99	Baseline: Mean 53.1 (SD 19) Followup: NR	NR	Comparator: Oxygen Difference in mean: - 1.56 (SD NR) (95% CI: -3.13, 0.02), p=NR	NR	Only pre data, and mean differences between groups reported
	Arm 2	Oxygen	PaCO2	mm Hg	Final: 48 hours	Baseline: 101 Followup: 101	Baseline: Mean 48.2 (SD 14) Followup: NR	NR	NA	NR	
Philip, 2006 <sup>21</sup> Respiratory vs Respiratory	Arm 1	Air first	Oxygen saturation	%	Final: 15 minutes	Baseline: 27 Followup: 27	Baseline: Median 93 (NR ), Range: 70-98 Followup: Median 93 (NR ), Range: 69- 98	NR	NR	NR	
	Arm 2	Oxygen first	Oxygen saturation	%	Final: 15 minutes	Baseline: 24 Followup: 24	Baseline: Median 93 (NR ), Range: 71-98 Followup: Median 97 (NR ), Range: 73- 100	NR	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Philip, 2006 <sup>21</sup> Respiratory vs Respiratory	Arm 1	Air first	Oxygen saturation	%	Final: 15 minutes	Baseline: 27 Followup: 27	Baseline: NR Followup: NR	Mean change from baseline: 0.94 (SD NR), p=NR	Comparator: Air first p<0.001	NR	
	Arm 2	Oxygen first	Oxygen saturation	%	Final: 15 minutes	Baseline: 24 Followup: 24	Baseline: NR Followup: NR	Mean change from baseline: 5.43 (SD NR), p=NR	NA	NR	
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	O2 sat before 6MWT	NR	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Median 93 (IQR 91 to 96) Followup: Median 92 (IQR 90 to 94)	Median change from baseline: NR, p=0.006	NR	NR	
	Arm 2	Acupressure	O2 sat before 6MWT	NR	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Median 92 (IQR 91 to 95) Followup: Median 95 (IQR 93 to 97)	Median change from baseline: NR, p≤0.001	NR	NR	
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	O2 sat after 6MWT	NR	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Median 90 (IQR 87 to 93) Followup: Median 88 (IQR 87 to 92)	Median change from baseline: NR, p=0.009	NR	NR	
	Arm 2	Acupressure	O2 sat after 6MWT	NR	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Median 89 (IQR 87 to 90) Followup: Median 93 (IQR 90 to 94)	Median change from baseline: NR, p≤0.001	NR	NR	
Wong, 2017 <sup>27</sup> Usual care vs Respiratory	Arm 1	Control	Oxygen saturation	%	Final: 5 minutes	Baseline: 15 Followup: 15	Baseline: Mean 95.47 (SD 3.4) Followup: NR	Mean change from baseline: -0.27 (SD 1.58), p=NR	NR	NR	For between group analysis- only p value given
	Arm 2	Fan	Oxygen saturation	%	Final: 5 minutes	Baseline: 15 Followup: 15	Baseline: Mean 93.4 (SD 8.31) Followup: NR	Mean change from baseline: 0 (SD 2.75), p=NR	NR	NR	

6MWT=6 minute talk test; CI=confidence interval; HFO=high flow oxygen; N=sample size; NIV=noninvasive ventilation; NR=not reported; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-27. Respiratory rate continuous outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kako, 2018 <sup>13</sup> Placebo vs Respiratory	Arm 1	Fan to legs (control)	Respiratory rate	RR per minute	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 14.6 (SD 4.2) Followup: Mean 14.7 (SD 4.2	Mean change from baseline: NR, p=0.716	SMD: -0.07 (95% CI: -0.69 to 0.55)	NR	
	Arm 2	Fan to face	Respiratory rate	RR per minute	Final: 5 minutes	Baseline: 20 Followup: 20	Baseline: Mean 17.8 (SD 4.8) Followup: Mean 17.6 (SD 4.6)	Mean change from baseline: NR, p=0.522	NA	NR	
Ting, 2020 <sup>24</sup> Placebo vs Respiratory	Arm 1	Placebo	Respiratory rate	RR per minute	Final: 5 minutes	Baseline: 24 Followup: 24	Baseline: NR Followup: NR	Mean change from baseline: -0.25 (SD 0.44), p=NR	Ref	NR	
	Arm 2	Fan on face	Respiratory rate	RR per minute	Final: 5 minutes	Baseline: 24 Followup: 24	Baseline: NR Followup: NR	Mean change from baseline: -1.88 (SD 0.94), p=NR	Comparator: Arm1 Difference in mean: p<0.0001 SMD: -2.22 (95% CI: -2.73 to -1.71)	NR	
Bruera, 1993 <sup>3</sup> Respiratory vs Respiratory	Arm 1	Air first	Respiratory rate	RR per minute	Final: 5 minutes	Baseline: 7 Followup: 7	Baseline: NR Followup: NR	Mean change from baseline: -0.5 (SD NR), (95% CI: -1.3, 0.3), p=0.25	SMD: 3.08 (95% CI: 1.46 to 4.70)	NR	
	Arm 2	Oxygen first	Respiratory rate	RR per minute	Final: 5 minutes	Baseline: 7 Followup: 7	Baseline: NR Followup: NR	Mean change from baseline: 3.5 (SD NR), (95% CI: 2.4, 4.6), p=0	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Respiratory rate	RR per minute	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Mean 22.1 (SD 6.4) Followup: Mean 20.1 (SD 4.8)	Mean change from baseline: -2.0 (SD 4), p=0.11	Comparator: High flow oxygen (HFO) Difference in mean: p=0.97 SMD: -0.22 (95% CI: -0.94 to 0.50)	NR	Between arm comparison of differences in means was limited to p value
	Arm 2	High flow oxygen (HFO)	Respiratory rate	RR per minute	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Mean 22.1 (SD 6.8) Followup: Mean 19.2 (SD 5.2)	Mean change from baseline: -3.0 (SD 5.2), p=0.11	NA	NR	
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Respiratory rate	RR per minute	Final: 48 hours	Baseline: 99 Followup: 99	Baseline: Mean 27.1 (SD 8) Followup: NR	NR	Comparator: Oxygen Difference in mean: - 0.75 (SD NR) (95% CI: -1.67, 0.18), p=NR	NR	Only pre data, and mean differences between groups reported
	Arm 2	Oxygen	Respiratory rate	RR per minute	Final: 48 hours	Baseline: 101 Followup: 101	Baseline: Mean 31.9 (SD 7.8) Followup: NR	NR	NA	NR	
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	RR before 6MWT	NR	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Mean 23.16 (SD 3.46) Followup: Mean 26.06 (SD 2.39)	Mean change from baseline: NR, p≤0.001	Comparator: Control p≤0.001 SMD: -1.73 (95% CI: -2.33 to -1.14)	NR	
	Arm 2	Acupressure	RR before 6MWT	NR	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Mean 24.75 (SD 4.35) Followup: Mean 21.65 (SD 2.88)	Mean change from baseline: NR, p≤0.001	NA	NR	
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	RR after 6MWT	NR	Final: 4 weeks	Baseline: 31 Followup: 31	Baseline: Mean 28.51 (SD 2.82) Followup: Mean 31.03 (SD 2.63)	Mean change from baseline: NR, p≤0.001	Comparator: Control p≤0.001 SMD: -2.16 (95% CI: -2.80 to -1.52)	NR	
	Arm 2	Acupressure	RR after 6MWT	NR	Final: 4 weeks	Baseline: 29 Followup: 29	Baseline: Mean 30.27 (SD 4.06) Followup: Mean 25.93 (SD 2.75)	Mean change from baseline: NR, p≤0.001	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Wong, 2017 <sup>27</sup> Usual care vs Respiratory	Arm 1	Control	Respiratory rate	RR per minute	Final: 5 minutes	Baseline: 15 Followup: 15	Baseline: Mean 22.67 (SD 4.5) Followup: NR	Mean change from baseline: -0.07 (SD 2.84), p=NR	Comparator: Control Difference in mean: p=0.491 SMD: -0.26 (95% CI: -0.98 to 0.46)	NR	For between group analysis- only p value given
	Arm 2	Fan	Respiratory rate	RR per minute	Final: 5 minutes	Baseline: 15 Followup: 15	Baseline: Mean 21.47 (SD 6.64) Followup: NR	Mean change from baseline: -0.79 (SD 2.69), p=NR	NA	NR	

6MWT=6 minute talk test; CI=confidence interval; N=sample size; NR=not reported; p=p-value; RR=respiratory rate; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-28. No adverse events reported for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Vanderbyl, 2017 <sup>25</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Standard exercise therapy	Any AE	NR	Final: 6 weeks	Followup: 13	Final FU: 0/13 (0)	NR	NR	NR	
	Arm 2	Qigong	Any AE	NR	Final: 6 weeks	Followup: 11	Final FU: 0/11 (0)	NR	NR	NR	
Kako, 2018 <sup>13</sup> Placebo vs Respiratory	Arm 1	Fan to legs (control)		Any AE	Final: 5 minutes	Followup: 20	Final FU: 0/20 (0)	NR	NR	NR	At 5 minutes (primary endpoint), dyspnea markedly better in fan to face arm. No dropout. No AE reported. No change in physiologic parameters.
	Arm 2	Fan to face		Any AE	Final: 5 minutes	Followup: 20	Final FU: 0/20 (0)	NR	NR	NR	
Booth, 1996 <sup>1</sup> Respiratory vs Respiratory	Arm 1	Air first		Any AE	Final: 15 minutes	Followup: 38	Final FU: 0/38 (0)	NR	NR	NR	At 15 min, no AE in any arm. This trial had crossover so check outcomes.
	Arm 2	Standard supplemental oxygen first		Any AE	Final: 15 minutes	Followup: 38	Final FU: 0/38 (0)	NR	NR	NR	
Hwang, 2012 <sup>12</sup> Usual care vs Activity/Rehab	Arm 1	Control		Any AE	Final: 8 weeks	Followup: 11	Final FU: 0/11 (0)	NR	NR	NR	
	Arm 2	Exercise		Any AE	Final: 8 weeks	Followup: 13	Final FU: 0/13 (0)	NR	NR	NR	

AE=adverse events; FU=followup; n=number of patients with events; N=sample size; NR=not reported



**Evidence Table D-29. Central nervous continuous outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Feel anxious	NRS (0-10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 2 (IQR 1.5, 4) Followup: Median 2 (IQR 0, 5)	Median change from baseline: 0 (SD NR), (IQR: -1, 0), p=0.69	Comparator: High flow oxygen (HFO) Difference in medians: p=0.12	NR	
	Arm 2	High flow oxygen (HFO)	Feel anxious	NRS (0-10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 1 (IQR 0, 5) Followup: Median 1 (IQR 0, 2)	Median change from baseline: 0 (SD NR), (IQR: -4, 0), p=0.69	NA	NR	

FU=followup; IQR=interquartile range; N=sample size; NR=not reported; NRS=numerical rating scale



**Evidence Table D-30. Central nervous categorical outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Seizure	NR	Final: 48 hours	Followup: 99	Final FU: 0/99 (0)	NR	RR: 2.94 (95% CI: 0.12 to 71.3)	NR	
	Arm 2	Oxygen	Seizure	NR	Final: 48 hours	Followup: 101	Final FU: 1/101 (1)	NR	NA	NR	
Molassiotis, 2015 <sup>16</sup> Usual care vs Respiratory	Arm 1	Control	Headache, dizziness (hypercapnia)	NR	Final: 12 weeks	Followup: 23	Final FU: 0/23 (0)	NR	RR: 8.64 (95% CI: 0.49 to 152.01)	NR	At 12 weeks (primary outcome), 36/ 47 (77%) had complete data, all 11 dropouts were death/ deterioration, rate of fatigue was 5% in IMT, but positive trial.
	Arm 2	Inspiratory muscle training (IMT)	Headache, dizziness (hypercapnia)	NR	Final: 12 weeks	Followup: 24	Final FU: 4/24 (16)	NR	NA	NR	Since all death, should not report as dropout. There are other AE to report.

AE=adverse events; CI=confidence interval; FU=followup; N=sample size; NR=not reported; RR=relative risk



**Evidence Table D-31. Death categorical outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	In-hospital death	NR	Final: In- hospital	Followup: 99	Final FU: 61/99 (61)	NR	Comparator: Oxygen HR: 0.67 (95% CI: 0.43 to 1.06), p=NR RR: 1.06 (95% CI: 0.86 to 1.31)	NR	
	Arm 2	Oxygen	In-hospital death	NR	Final: In- hospital	Followup: 101	Final FU: 66/101 (66)	NR	NA	NR	

AE=adverse events; CI=confidence interval; FU=followup; N=sample size; NR=not reported; RR=relative risk



**Evidence Table D-32. Discomfort continuous outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Dry eyes	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 1.5 (IQR 0, 4) Followup: Median 0 (IQR 0, 4)	Median change from baseline: 0 (SD NR), (IQR: - 1, 0), p=0.63	Comparator: High flow oxygen (HFO) Difference in medians: p=0.1	NR	
	Arm 2	High flow oxygen (HFO)	Dry eyes	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 3 (IQR 0, 4) Followup: Median 0 (IQR 0, 3)	Median change from baseline: 0 (SD NR), (IQR: - 3, 0), p=0.22	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Eye irritation	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 1 (IQR 0, 3) Followup: Median 0 (IQR 0, 3)	Median change from baseline: 0 (SD NR), (IQR: - 1, 0), p=0.22	Comparator: High flow oxygen (HFO) Difference in medians: p=0.47	NR	
	Arm 2	High flow oxygen (HFO)	Eye irritation	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 3 (IQR 0, 4) Followup: Median 0 (IQR 0, 1)	Median change from baseline: 0 (SD NR), (IQR: - 3, 0), p=0.13	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Mask painful	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 0 (IQR 0, 2) Followup: Median 1 (IQR 0, 3)	Median change from baseline: 1.5 (SD NR), (IQR: 0,3), p>0.99	Comparator: High flow oxygen (HFO) Difference in medians: p=0.3	NR	
	Arm 2	High flow oxygen (HFO)	Mask painful	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median NA (IQR ) Followup: Median NA (IQR NA)	Median change from baseline: NA	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Moist mouth	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 2 (IQR 1.5, 2) Followup: Median 0 (IQR 0, 2)	Median change from baseline: - 1.5 (SD NR), (IQR: -2, 0), p=0.13	Comparator: High flow oxygen (HFO) Difference in medians: p=0.32	NR	
	Arm 2	High flow oxygen (HFO)	Moist mouth	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 2 (IQR 0, 5) Followup: Median 5 (IQR 1, 7)	Median change from baseline: 0 (SD NR), (IQR: -1, 0), p=0.73	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Prong uncomfortabl e	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 2 (IQR 0, 5) Followup: Median 0 (IQR 0, 0)	Median change from baseline: - 2.5 (SD NR), (IQR: -5, 0), p=>0.99	Comparator: High flow oxygen (HFO) Difference in medians: p=0.12	NR	
	Arm 2	High flow oxygen (HFO)	Prong uncomfortabl e	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 2 (IQR 0, 5.5) Followup: Median 2 (IQR 0, 4)	Median change from baseline: 0 (SD NR), (IQR: -1, 2), p=0.73	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Suffocation	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 1.5 (IQR 0, 5) Followup: Median 0 (IQR 0, 3)	Median change from baseline: - 1 (SD NR), (IQR: -3, 0), p=0.22	Comparator: High flow oxygen (HFO) Difference in medians: p=0.58	NR	
	Arm 2	High flow oxygen (HFO)	Suffocation	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 1.5 (IQR 0, 7) Followup: Median 1.5 (IQR 0, 4)	Median change from baseline: 0 (SD NR), (IQR: -1, 0), p>0.99	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Trouble drinking	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 1.5 (IQR 0, 2.5) Followup: Median 3 (IQR 0, 7)	Median change from baseline: 1 (SD NR), (IQR: -2, 5), p=0.51	Comparator: High flow oxygen (HFO) Difference in medians: p=0.46	NR	
	Arm 2	High flow oxygen (HFO)	Trouble drinking	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 0 (IQR 0, 5) Followup: Median 0 (IQR 0, 3)	Median change from baseline: 0 (SD NR), (IQR: 0, 1), p>0.99	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Trouble eating	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 2.5 (IQR 1, 5.5) Followup: Median 3 (IQR 0, 5)	Median change from baseline: - 1 (SD NR), (IQR: -3, 3), p=0.75	Comparator: High flow oxygen (HFO) Difference in medians: p=0.87	NR	
	Arm 2	High flow oxygen (HFO)	Trouble eating	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 5 (IQR 0, 7) Followup: Median 2 (IQR 0, 6)	Median change from baseline: 0 (SD NR), (IQR: -1, 0), p=0.69	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Trouble sleeping	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 2 (IQR 0.5, 4.5) Followup: Median 2 (IQR 0, 7)	Median change from baseline: 0 (SD NR), (IQR: -1, 3), p>0.99	Comparator: High flow oxygen (HFO) Difference in medians: p=0.02	NR	
	Arm 2	High flow oxygen (HFO)	Trouble sleeping	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 7 (IQR 6, 8) Followup: Median 1 (IQR 0, 6)	Median change from baseline: - 6 (SD NR), (IQR: -8, 0), p=0.04	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Trouble talking	NRS (0- 10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 2 (IQR 0.5, 3.5) Followup: Median 5 (IQR 2, 7)	Median change from baseline: 0 (SD NR), (IQR: 0, 5), p=0.45	Comparator: High flow oxygen (HFO) Difference in medians: p=0.004	NR	
	Arm 2	High flow oxygen (HFO)	Trouble talking	NRS (0- 10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 6 (IQR 2, 8) Followup: Median 2 (IQR 0, 6)	Median change from baseline: 0 (SD NR), (IQR: -6, 2), p=0.73	NA	NR	

IQR=interquartile range; N=sample size; NA=not available; NRS=numerical rating scale; p=p-value; SD=standard deviation



**Evidence Table D-33. Discomfort categorical outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Claustrophobia, suffocation, anxiety/ sweating, sense of imminent death	NR	Final: 48 hours	Followup: 99	Final FU: 14/99 (14)	NR	RR: 0.42 (95% CI: 0.17 to 1.05)	NR	
	Arm 2	Oxygen	Claustrophobia, suffocation, anxiety/ sweating, sense of imminent death	NR	Final: 48 hours	Followup: 101	Final FU: 6/101 (6)	NR	NA	NR	
Dogan, 2019 <sup>8</sup> Usual care vs Integrative medicine interventions	Arm 1	Control	Sensitivity, ecchymosis, pain in region of acupressure	NR	Final: 4 weeks	Followup: 38	Final FU: 0/38 (0)	NR	RR: 5.0 (95% CI: 0.25 to 100.80)	NR	At 4 weeks (primary endpoint), 31/ 38 in control and 29/ 38 in acupressure arm completed. 31 and 29 included in final analysis.
	Arm 2	Acupressure	Sensitivity, ecchymosis, pain in region of acupressure	NR	Final: 4 weeks	Followup: 38	Final FU: 2/38 (5.2)	NR	NA	NR	Of 7 dropouts in control-- 2 death, 1 no want 6mwt, 2 uncontact, 2 did not want interview. Of 9 dropouts in acupressure, 1 death, 2 other health issues, 1 psych trauma from family member death, remaining 5= 2 side effect, 3 unable/ did not want to continue acupressure
Molassiotis, 2015 <sup>16</sup> Usual care vs Respiratory	Arm 1	Control	Fatigue, chest muscle soreness,	NR	Final: 12 weeks	Followup: 23	Final FU: 0/23 (0)	NR	RR: 24 (95% CI: 1.50 to 383.26)	NR	
	Arm 2	Inspiratory muscle training (IMT)	Fatigue, chest muscle soreness,	NR	Final: 12 weeks	Followup: 24	Final FU: 12/24 (50)	NR	NA	NR	

CI=confidence interval; FU=follow-up; N=sample size; NR=not reported; RR=relative risk; SD=standard deviation



**Evidence Table D-34. Dropout categorical outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Henke, 2014 <sup>10</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Control	Non-compliance	NR	Final: 9 weeks	Followup: 20	Final FU: 7/20 (35)	NR	RR: 0.12 (95% CI: 0.02 to 0.89)	NR	At 9 weeks (primary endpoint), 29 patients gave data. Of the 2/ 24 who started, 11/18 completed. 7/2 in control and 1/24 in exercise were non-compliant. Rest 7 were deaths or ongoing treatment. Therefore total retention was 29/ 44 (66%). All outcomes improved in intervention.
	Arm 2	Intervention	Non-compliance	NR	Final: 9 weeks	Followup: 24	Final FU: 1/24 (4)	NR	NA	NR	
Vanderbyl, 2017 <sup>25</sup> Activity/Rehab vs Activity/Rehab	Arm 1	Standard exercise therapy	Combo of death/ loss of interest/ change in medical condition	NR	Final: 6 weeks	Followup: 17	Final FU: 4/17 (24)	NR	RR: 1.79 (95% CI: 0.65 to 4.89)	NR	At 6 weeks (primary endpoint), 12/ 36 who started did not continue due to combo outcome (did not separate), so attrition was 33.3%. No other AE. Baseline data only for 24 people who completed trial. Then 2 week crossover and 6 weeks more. 5 more patients dropped out, so final attrition after 14 weeks (6 week, 2 week washout, 6 more weeks) was 17/36 47%. Adherence to in-person sessions was 75% in QG, 87% in SET (p .9) and report mean enjoyment 9-9.1/ 1 for both groups.
	Arm 2	Qigong	Combo of death/ loss of interest/ change in medical condition	NR	Final: 6 weeks	Followup: 19	Final FU: 8/19 (42)	NR	NA	NR	Dropouts were composite outcome (don't know exact split of attrition).



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Mosher, 2019 <sup>18</sup> Behavioral/Psych vs Behavioral/Psych+ Integrative medicine interventions	Arm 1	Education/ support	Lack of interest	NR	Final: 6 weeks	Followup: 25	Final FU: 1/25 (4)	NR	RR: 1 (95% CI: 0.07 to 15.12)	NR	At 6 weeks (primary endpoint), 7/25 in control and 5/25 in ACT arm had no data, mostly due to death/ medical reasons. Overall attrition rate, 12/5= 24%, retention rate 76% at 6 weeks. At 6 weeks (primary endpoint), 19/25 in control and 2/25 in ACT arm had completed 6/6 sessions of phone calls. Overall adherence 78%. Both groups showed minimal change over time, with no between group differences.
	Arm 2	Acceptance and Commitme nt Therapy (ACT)	Lack of interest	NR	Final: 6 weeks	Followup: 25	Final FU: 1/25 (4)	NR	NA	NR	
Vickers, 2005 <sup>26</sup> Placebo vs Integrative medicine interventions	Arm 1	Control	Loss to follow-up	NR	Final: 7 days	Followup: 21	Final FU: 1/21 (4)	NR	RR: 0.28 (95% CI: 0.01 to 6.58)	NR	At 1 week (primary endpoint), 45/46 patients had follow up data, only 1 lost to follow-up. Attrition 2%. Adherence 1%. Acupuncture worse than placebo at 1 day and at 1 week.
	Arm 2	Acupunctur e/ acupressur e	Loss to follow-up	NR	Final: 7 days	Followup: 25	Final FU: 0/25 (0)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 2003 <sup>4</sup> Respiratory vs Respiratory	Arm 1	Air	Personal reasons/ time constraints	NR	Final: 6 minutes	Followup: 17	Final FU: 0/17 (0)	NR	RR: 3 (95% CI: 0.13 to 68.84)	NR	At 11 minutes, only 1/34 had dropout (personal time constraints), 33/34 completed. Oxygen not effective.
	Arm 2	Standard supplement al oxygen	Personal reasons/ time constraints	NR	Final: 6 minutes	Followup: 17	Final FU: 1/17 (6)	NR	NA	NR	
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Discontinued treatment	NR	Final: 2 hours	Followup: 15	Final FU: 5/15 (33)	NR	RR: 0.4 (95% CI: 0.09 to 1.75)	NR	At primary endpoint (2 hours), 23/ 3 completed trial (77%), no difference between arms in dropout. Medical side effects given in continuous table, only one significant is trouble sleeping (better in HFO).
	Arm 2	High flow oxygen (HFO)	Discontinued treatment	NR	Final: 2 hours	Followup: 15	Final FU: 2/15 (13)	NR	NA	NR	
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasiv e ventilation (NIV)	Discontinued treatment	NR	Final: 48 hours	Followup: 99	Final FU: 11/99 (11.1)	NR	RR: 0.04 (95% CI: 0 to 0.71)	NR	At primary endpoint (2 hours), 11/99 (11%) in NIV arm dropped out, mostly anxiety/ tolerance. Some other AE s. They also reported in hospital death but these were later than in study. Overall NIV was more effective. Important outcome (unique to this study) was reduction in opioid dose.
	Arm 2	Oxygen	Discontinued treatment	NR	Final: 48 hours	Followup: 101	Final FU: 0/101 (0)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hwang, 2012 <sup>12</sup> Usual care vs Activity/Rehab	Arm 1	Control	Personal reasons/ time constraints	NR	Final: 8 weeks	Followup: 11	Final FU: 2/11 (18)	NR	RR: 0.42 (95% CI: 0.04 to 4.06)	NR	At 8 weeks (primary outcome), 18/24 (75%) gave assessment, the 6 dropouts across arms was change in treatment (3) and personal reasons (3). In exercise arms, out of 24 total sessions, mean attendance was 71%, 9/13 patients attended 75% sessions and 3/13 attending all 24. All missed sessions were due to medical reasons and no AE occurred.
	Arm 2	Exercise	Personal reasons/ time constraints	NR	Final: 8 weeks	Followup: 13	Final FU: 1/13 (8)	NR	NA	NR	
Chan, 2011 <sup>5</sup> Usual care vs Activity/Rehab+ Behavioral/Psych	Arm 1	Control	All dropouts= death	NR	Final: 12 weeks	Followup: 70	Final FU: 30/70 (42)	NR	RR: 0.27 (95% CI: 0.13 to 0.54)	NR	At 12 weeks, attrition rate 27%, all due to death which was higher in control (42%) vs PEI arm (1%). PEI effective. 94% had ful adherence as reported in dairy. >6% listened to audiotape and read leaflets. Avg practiced PMR 4-5x/ week.
	Arm 2	Psychoedu cational intervention (PEI)	All dropouts= death	NR	Final: 12 weeks	Followup: 70	Final FU: 8/70 (11)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Corner, 1996 <sup>6</sup> Usual care vs Activity/Rehab+ Behavioral/Psych	Arm 1	Control	All dropouts= death/ deterioration	NR	Final: 12 weeks	Followup: 15	Final FU: 6/15 (40)	NR	RR: 1.05 (95% CI: 0.47 to 2.38)	NR	At 12 weeks, 2 patients for whom baseline data was available completed study. 34 had started, 14/34 (41%) clinically deteriorated. No dropout due to anything else. Overall positive results, more so at 12 weeks than 4 weeks.
	Arm 2	Nurse led intervention	All dropouts= death/ deterioration	NR	Final: 12 weeks	Followup: 19	Final FU: 8/19 (42.1)	NR	NA	NR	
Farquhar, 2014 <sup>9</sup> Usual care vs Activity/Rehab+ Behavioral/Psych+ Integrative medicine interventions	Arm 1	Control	Loss to follow-up	NR	Final: 2 weeks	Followup: 32	Final FU: 0/32 (0)	NR	RR: Zero events	NR	At 2 weeks (primary outcome), 13/67 (19%) had died/ deteriorated, that was only loss to f/u. 54/67 completed study. This was a positive study. This was a crossover study where control arm then underwent BIS but full data NR.
	Arm 2	Intervention	Loss to follow-up	NR	Final: 2 weeks	Followup: 35	Final FU: 0/35 (0)	NR	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Yorke, 2015 <sup>29</sup> Usual care vs Activity/Rehab+ Behavioral/Psych+ Integrative medicine interventions	Arm 1	Usual care	Includes deaths/ sickness/ loss of follow up	NR	Final: 12 weeks	Followup: 51	Final FU: 11/51 (22)	NR	RR: 1.76 (95% CI: 0.94 to 3.31)	NR	At 12 weeks (primary outcome), dropout was 3/11 (7/11 provided data), therefore attrition was 3% (more in RDSI, 38% than control 24%). Causes of attrition varied (of the 3 dropouts, 12 deaths and sickness, and 18 declined and loss of follow up). They also reported multiple other outcomes (worst / relief/ distress unpleasant coping breathlessness).
	Arm 2	Respiratory Distress Symptom Intervention (RDSI)	Includes deaths/ sickness/ loss of follow up	NR	Final: 12 weeks	Followup: 50	Final FU: 19/50 (38)	NR	NA	NR	Adherence= daily breathing exercises >87% of patients, acupressure> 84%, cough practiced daily 36-54%
Bordeleau, 2003 <sup>2</sup> Usual care vs Behavioral/Psych	Arm 1	Control	Mostly death but don't know	NR	Final: 12 months	Followup: 70	Final FU: 52/70 (74)	NR	RR: 0.85 (95% CI: 0.71 to 1.03)	NR	At 12 months (primary outcome), 71/215 completed assessment (33%). Of total sessions, attendance was 66.7%- most missed due to illness/ ongoing treatment., and total Questionnaire completion rate was 66%. Rate of death NR. Overall, all symptoms worsened over time in both arms, and no difference between arms.
	Arm 2	Intervention	Mostly death but don't know	NR	Final: 12 months	Followup: 145	Final FU: 92/145 (63)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
McMillan, 2007 <sup>15</sup> Usual care vs Behavioral/Psych	Arm 1	Standard care	Mostly death but don't know	NR	Final: 30 days	Followup: 109	Final FU: 78/109 (72)	NR	RR: 0.89 (95% CI: 0.74 to 1.07)	NR	At 3 days (primary endpoint), only 12/ 329 provided info (69% attrition) but this was a hospice-- attrition was mostly deaths but not exactly stated. HOPE intervention improved "symptom distress" but not dyspnea or QOL scores
	Arm 3	Standard care and COPE	Mostly death but don't know	NR	Final: 30 days	Followup: 111	Final FU: 71/111 (64)	NR	NA	NR	
McMillan, 2007 <sup>15</sup> Usual care vs Behavioral/Psych	Arm 1	Standard care	Mostly death but don't know	NR	Final: 30 days	Followup: 109	Final FU: 78/109 (72)	NR	RR: 0.99 (95% CI: 0.83 to 1.17)	NR	At 3 days (primary endpoint), only 12/ 329 provided info (69% attrition) but this was a hospice-- attrition was mostly deaths but not exactly stated. HOPE intervention improved "symptom distress" but not dyspnea or QOL scores
	Arm 2	Standard care and support	Mostly death but don't know	NR	Final: 30 days	Followup: 109	Final FU: 77/109 (71)	NR	NA	NR	
Moore, 2002 <sup>17</sup> Usual care vs Behavioral/Psych	Arm 1	Control	Loss to follow-up	NR	Final: 3 months	Followup: 103	Final FU: 1/103 (1)	NR	RR: 6.24 (95% CI: 0.77 to 50.92)	NR	At 3 months (primary endpoint), 156/23 (77%) had follow up data- only 7 (4%) lost to follow-up, rest death or ill health. At 12 months, 6/ 23 (3%) had follow-up data, 7% patients died during study. Nurse led group had stable dyspnea score, while control arm had worsening.
	Arm 2	Nurse-led intervention	Loss to follow-up	NR	Final: 3 months	Followup: 99	Final FU: 6/99 (6)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
McMillan, 2007 <sup>15</sup> Behavioral/Psych vs Behavioral/Psych	Arm 2	Standard care and support	Mostly death but don't know	NR	Final: 30 days	Followup: 109	Final FU: 77/109 (71)	NR	RR: 0.91 (95% CI: 0.75 to 1.09)	NR	
	Arm 3	Standard care and COPE	Mostly death but don't know	NR	Final: 30 days	Followup: 111	Final FU: 71/111 (64)	NR	NA	NR	
Wyatt, 2012 <sup>28</sup> Integrative Medicine Interventions vs Integrative Medicine Interventions	Arm 2	Lay foot manipulation	Don't know cause	NR	Final: 11 weeks	Followup: 95	Final FU: 28/95 (29)	NR	RR: 0.86 (95% CI: 0.54 to 1.36)	NR	
	Arm 3	Reflexology	Don't know cause	NR	Final: 11 weeks	Followup: 95	Final FU: 24/95 (25)	NR	NA	NR	
Dogan, 2019 <sup>8</sup> Usual care vs Integrative Medicine Interventions	Arm 1	Control	Did not complete	NR	Final: 4 weeks	Followup: 38	Final FU: 7/38 (18.4)	NR	RR: 1.29 (95% CI: 0.53 to 3.1)	NR	
	Arm 2	Acupressure	Did not complete	NR	Final: 4 weeks	Followup: 38	Final FU: 9/38 (23.7)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative Medicine Interventions	Arm 1	Control	Don't know cause	NR	Final: 11 weeks	Followup: 96	Final FU: 33/96 (35)	NR	RR: 0.73 (95% CI: 0.47 to 1.14)	NR	At 11 weeks, approx 3% attrition but unclear cause (deaths vs others-- no difference between groups, exact cause not stated).9% of women in LFM arm and 89% of women in reflexology arms completed 4/4 sessions, >92% of women in both arms completed at least 3/4 sessions. Reflexology is helpful.
	Arm 3	Reflexology	Don't know cause	NR	Final: 11 weeks	Followup: 95	Final FU: 24/95 (25)	NR	NA	NR	
Wyatt, 2012 <sup>28</sup> Usual care vs Integrative Medicine Interventions	Arm 1	Control	Don't know cause	NR	Final: 11 weeks	Followup: 96	Final FU: 33/96 (35)	NR	RR: 0.86 (95% CI: 0.57 to 1.3)	NR	At 11 weeks, approx 3% attrition but unclear cause (deaths vs others-- no difference between groups, exact cause not stated).9% of women in LFM arm and 89% of women in reflexology arms completed 4/4 sessions, >92% of women in both arms completed at least 3/4 sessions. Reflexology is helpful.
	Arm 2	Lay foot manipulation	Don't know cause	NR	Final: 11 weeks	Followup: 95	Final FU: 28/95 (29)	NR	NA	NR	
Molassiotis, 2015 <sup>16</sup> Usual care vs Respiratory	Arm 1	Control	All dropouts= death/ deterioration	NR	Final: 12 weeks	Followup: 23	Final FU: 5/23 (22)	NR	RR: 1.15 (95% CI: 0.41 to 3.25)	NR	
	Arm 2	Inspiratory muscle training (IMT)	All dropouts= death/ deterioration	NR	Final: 12 weeks	Followup: 24	Final FU: 6/24 (25)	NR	NA	NR	

Activity/Rehab=activity and rehabilitation intervention; Behavioral/Psych=behavioral and psychoeducational intervention; CI=confidence interval; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation; SE=standard error



**Evidence Table D-35. Dry mouth categorical outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Dry throat	NR	Final: 48 hours	Followu p: 99	Final FU: 6/99 (6)	NR	RR: 0.16 (95% CI: 0.02 to 1.33)	NR	
	Arm 2	Oxygen	Dry throat	NR	Final: 48 hours	Followu p: 101	Final FU: 1/101 (1)	NR	NA	NR	

CI=confidence interval; n=number of patients with events; N=sample size; NR=not reported; RR=relative risk



Evidence Table D-36. Gastrointestinal continuous outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients											
Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2013 <sup>11</sup> Respiratory vs Respiratory	Arm 1	Bilevel positive airway pressure (BiPAP)	Stomach bloating	NRS (0-10)	Final: 2 hours	Baseline: 16 Followup: 16	Baseline: Median 1 (IQR 0, 3) Followup: Median 0 (IQR 0, 1)	Median change from baseline: -1 (SD NR), (IQR: - 2, 0), p=0.13	Comparator: High flow oxygen (HFO) Difference in medians: p=0.82	NR	
	Arm 2	High flow oxygen (HFO)	Stomach bloating	NRS (0-10)	Final: 2 hours	Baseline: 14 Followup: 14	Baseline: Median 3 (IQR 0, 6) Followup: Median 2 (IQR 0, 4)	Median change from baseline: - 0.5 (SD NR), (IQR: -1, 0), p=0.22	NA	NR	

CI=confidence interval; IQR=interquartile range; n=number of patients with events; N=sample size; NR=not reported; NRS=Numerical Rating Scale; p=p-value; SD=standard deviation



Evidence Table D-37. Gastrointestinal categorical outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients											
Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Nausea, vomiting, constipation	NR	Final: 48 hours	Followup: 99	Final FU: 9/99 (9)	NR	RR: 1.09 (95% CI: 0.46 to 2.57)	NR	
	Arm 2	Oxygen	Nausea, vomiting, constipation	NR	Final: 48 hours	Followup: 101	Final FU: 10/101 (10)	NR	NA	NR	

CI=confidence interval; n=number of patients with events; N=sample size; NR=not reported; RR=relative risk



**Evidence Table D-38. Pruritis categorical outcomes for studies comparing nonpharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Itching	NR	Final: 48 hours	Followup: 99	Final FU: 2/99 (2)	NR	RR: 0.49 (95% CI: 0.05 to 5.32)	NR	
	Arm 2	Oxygen	Itching	NR	Final: 48 hours	Followup: 101	Final FU: 1/101 (1)	NR	NA	NR	

CI=confidence interval; n=number of patients with events; N=sample size; NR=not reported; RR=relative risk



Evidence Table D-39. Urinary retention categorical outcomes for studies comparing non-pharmacological interventions for treating breathlessness in advanced cancer patients											
Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Nava, 2013 <sup>20</sup> Respiratory vs Respiratory	Arm 1	Noninvasive ventilation (NIV)	Urinary retention	NR	Final: 48 hours	Followup: 99	Final FU: 0/99 (0)	NR	RR: 4.90 (95% CI: 0.24 to 100.83)	NR	
	Arm 2	Oxygen	Urinary retention	NR	Final: 48 hours	Followup: 101	Final FU: 2/101 (2)	NR	NA	NR	

CI=confidence interval; n=number of patients with events; N=sample size; NR=not reported; RR=relative risk



**Evidence Table D-40. Anxiety continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hardy, 2016 <sup>36</sup> Anxiolytics vs Placebo	Arm 1	Placebo	Anxiety	NRS	NR	NR	NR	NR	Ref	NR	Only reported no difference between arms
	Arm 2	Midazolam hydrochlor ide	Anxiety	NRS	NR	NR	NR	NR	Comparator: Arm 1 p=NS	NR	Only reported no difference between arms
Peoples, 2016 <sup>45</sup> Anxiolytics vs Placebo	Arm 1	Placebo	Anxiety, complete case	Spielberger State-Trait Anxiety Inventory (STAI-S)	Final: 28 days	Baseline: 192 Followup: 155	Baseline: Mean 40.9 (SD NR) Followup: NR	NR	Ref	Clinic site	Complete case only
	Arm 2	Buspirone	Anxiety, complete case	Spielberger State-Trait Anxiety Inventory (STAI-S)	Final: 28 days	Baseline: 187 Followup: 156	Baseline: Mean 40.5 (SD NR) Followup: NR	NR	Comparator: Arm 1 Estimate, not specified: 1.83 (SE 0.98)(95% CI: -0.092 to 3.746), p=0.062	Clinic site	Complete case only
Peoples, 2016 <sup>45</sup> Anxiolytics vs Placebo	Arm 1	Placebo	Anxiety, multiple imputation estimate	Spielberger State-Trait Anxiety Inventory (STAI-S)	Final: 28 days	Baseline: 192 Followup: 192	Baseline: Mean 40.9 (SD NR) Followup: Mean 38.6 (SD NR)	NR	Ref	Clinic site	Multiple imputation only
	Arm 2	Buspirone	Anxiety, multiple imputation estimate	Spielberger State-Trait Anxiety Inventory (STAI-S)	Final: 28 days	Baseline: 187 Followup: 187	Baseline: Mean 40.5 (SD NR) Followup: Mean 40.1 (SD NR)	NR	Comparator: Arm 1 Estimate, not specified: 1.74 (SE 1.06)(95% CI: -0.336 to 3.823), p=0.1	Clinic site	Multiple imputation only

CI=confidence interval; n=number of patients with events; N=sample size; NR=not reported



**Evidence Table D-41. Breathlessness continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Anxiolytics vs Combination	Arm 2	Midazolam	Dyspnea intensity	Borg scale	Final: 48 hours	Baseline: 33 Followup: 23	Baseline: Mean 6.9 (SD 1) Followup: Median 2 (SD NR), IQR: 0 to 7	NR: p=0.004	Comparator: NR p=NS	NR	Baseline only reported in means and SD: Arm 2 is either 0.0004 or 0.004 (different in the text vs the figure legend)
	Arm 3	Morphine+ Midazolam	Dyspnea intensity	Borg scale	Final: 48 hours	Baseline: 33 Followup: 23	Baseline: Mean 6.8 (SD 0.8) Followup: Median 2 (SD NR), IQR: 1 to 5	NR: p<0.0001	Comparator: NR p=NS	NR	Baseline only reported in means and SD
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Dyspnea	Numeric Rating Scale	Final: 5 days	Baseline: 31 Followup: 30	Baseline: Median 9 (Median absolute deviation: 0) Followup: Median 6 (Median absolute deviation: 1)	Median change from baseline: p<0.001	NR	NR	
	Arm 2	Midazolam	Dyspnea	Numeric Rating Scale	Final: 5 days	Baseline: 32 Followup: 31	Baseline: Median 9 (Median absolute deviation: 0) Followup: Median 4.5 (Median absolute deviation: 1.5)	Median change from baseline: p<0.001	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Dyspnea intensity	Numeric Rating Scale	Final: 5 days	Baseline: 31 Followup: 30	Baseline: Median 8.6 (SD NR), Range: 8.1 to 10 Followup: Median 6 (SD NR), Range: 2.9 to 9.1	Median change from baseline: p=0.83	Ref	NR	
	Arm 2	Midazolam	Dyspnea intensity	Numeric Rating Scale	Final: 5 days	Baseline: 32 Followup: 31	Baseline: Median 9.12 (SD NR), Range: 7.1 to 10 Followup: Median 4 (SD NR), Range: 0 to 7.1	Median change from baseline: p=0.31	Comparator: Arm1 p≤0.001	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	BTD episodes	NR	Final: 5 days	Baseline: 30 Followup: 30	Baseline: Mean 1.9 (SD NR), 95% CI: 1.4 to 2.3 Followup: Mean 1.9 (SD NR), 95% CI: 1.2 to 2.5	NR	NR	NR	
	Arm 2	Midazolam	BTD episodes	NR	Final: 5 days	Baseline: 31 Followup: 31	Baseline: Mean 1.9 (SD NR), 95% CI: 1.4 to 2.2 Followup: Mean 0.6 (SD NR), 95% CI: 0.3 to 0.8	NR	NR	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Dyspnea intensity	Borg scale	Final: 48 hours	Baseline: 35 Followup: 24	Baseline: Mean 7.1 (SD 0.8) Followup: Median 2 (SD NR), IQR: 0 to 4.7	NR: p=0.0001	Comparator: NR p=NS	NR	Baseline only reported in means and SD
	Arm 2	Midazolam	Dyspnea intensity	Borg scale	Final: 48 hours	Baseline: 33 Followup: 23	Baseline: Mean 6.9 (SD 1) Followup: Median 2 (SD NR), IQR: 0 to 7	NR: p=0.004	Comparator: NR p=NS	NR	Baseline only reported in means and SD: Arm 2 is either 0.0004 or 0.004 (different in the text vs the figure legend)



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Opioids vs Combination	Arm 1	Morphine	Dyspnea intensity	Borg scale	Final: 48 hours	Baseline: 35 Followup: 24	Baseline: Mean 7.1 (SD 0.8) Followup: Median 2 (SD NR), IQR: 0 to 4.7	NR: p=0.0001	Comparator: NR p=NS	NR	Baseline only reported in means and SD
	Arm 3	Morphine+ Midazolam	Dyspnea intensity	Borg scale	Final: 48 hours	Baseline: 33 Followup: 23	Baseline: Mean 6.8 (SD 0.8) Followup: Median 2 (SD NR), IQR: 1 to 5	NR: p<0.0001	Comparator: NR p=NS	NR	Baseline only reported in means and SD
Tian, 2016 <sup>48</sup> Corticosteroids vs Bronchodilators	Arm 2	Methylpred nisolone	Dyspnea	VAS	Final: 1 hour	Baseline: 111 Followup: 111	Baseline: Mean 64.04 (SD 12.09) Followup: Mean 25.72 (SD 15.03)	NR	NR SMD: 0.41 (95% CI: 0.15 to 0.68)	NR	There is a discrepancy between the text and the table for methylpred VAS after treatment. In text it is 25.72 +/- 15.03. In the table it is 24.58 +/- 17.51. Recorded the text number. p=0.000, comparing VAS after treatment (not change from baseline)
	Arm 3	Aminophylli ne	Dyspnea	VAS	Final: 1 hour	Baseline: 114 Followup: 114	Baseline: Mean 64.43 (SD 11.86) Followup: Mean 31.95 (SD 16)	NR	NA	NR	p=0.000, comparing VAS after treatment (not change from baseline)
Tian, 2016 <sup>48</sup> Opioids vs Bronchodilators	Arm 1	Morphine	Dyspnea	VAS	Final: 1 hour	Baseline: 118 Followup: 118	Baseline: Mean 65.06 (SD 13.27) Followup: Mean 16.82 (SD 10.89)	NR	NR SMD: 1.18 (95% CI: 0.90 to 1.46)	NR	p=0.000, comparing VAS after treatment (not change from baseline)
	Arm 3	Aminophylli ne	Dyspnea	VAS	Final: 1 hour	Baseline: 114 Followup: 114	Baseline: Mean 64.43 (SD 11.86) Followup: Mean 31.95 (SD 16)	NR	NA	NR	p=0.000, comparing VAS after treatment (not change from baseline)



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Tian, 2016 <sup>48</sup> Opioids vs Corticosteroids	Arm 1	Morphine	Dyspnea	VAS	Final: 1 hour	Baseline: 118 Followup: 118	Baseline: Mean 65.06 (SD 13.27) Followup: Mean 16.82 (SD 10.89)	NR	NR SMD: 0.76 (95% CI: 0.49 to 1.03)	NR	p=0.000, comparing VAS after treatment (not change from baseline)
	Arm 2	Methylpred nisolone	Dyspnea	VAS	Final: 1 hour	Baseline: 111 Followup: 111	Baseline: Mean 64.04 (SD 12.09) Followup: Mean 25.72 (SD 15.03)	NR	NA	NR	
Aabom, 2019 <sup>30</sup> Opioids vs Opioids	Arm 1	Red morphine drops	Breathlessne ss	NRS	Final: 20 minutes Primary: 3 minutes	Baseline: 12 Followup: 12 Primary: 12	Baseline: Mean 100 (SD NR) Followup: Mean 5.49 (SD NR) Primary: Mean 39.19 (SD NR)	NR	Ref	NR	
	Arm 2	Morphine sulfate	Breathlessne ss	NRS	Final: 20 minutes Primary: 3 minutes	Baseline: 12 Followup: 12 Primary: 12	Baseline: Mean 100 (SD NR) Followup: Mean 2.93 (SD NR) Primary: Mean 54.21 (SD NR)	NR	Comparator: Arm1 Primary, 3minutes: p<0.05 Followup, 20 minutes: p=NS	NR	
Allard, 1999 <sup>31</sup> Opioids vs Opioids	Arm 1	Opioid dose 25% of 4 hourly regular dose	Dyspnea intensity	VAS	Final: 240 minutes	Baseline: 18 Followup: 18	Baseline: Mean 4.6 (SD NR) Followup: Mean 3.6 (SD NR)	NR	NR	NR	Followup data from figure, not text
	Arm 2	Opioid dose 50% of 4 hourly regular dose	Dyspnea intensity	VAS	Final: 240 minutes	Baseline: 15 Followup: 15	Baseline: Mean 4.4 (SD NR) Followup: Mean 3.4 (SD NR)	NR	NR	NR	Followup data from figure, not text



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 2005 <sup>33</sup> Opioids vs Opioids	Arm 1	Subcutane ous morphine	Dyspnea intensity	0-10 scale (not specified)	Final: 60 min	Baseline: 11 Followup: 11	Baseline: Median 5 (SD NR), Range: 3 to 8 Followup: Median 3 (SD NR), Range: 0 to 7	Median change from baseline: p=0.025	Comparator: Not specified p=NS	NR	0=no dyspnea, 10=worst possible dyspnea.
	Arm 2	Nebulized morphine	Dyspnea intensity	0-10 scale (not specified)	Final: 60 min	Baseline: 11 Followup: 11	Baseline: Median 4 (SD NR), Range: 3 to 9 Followup: Median 2 (SD NR), Range: 0 to 9	Median change from baseline: p=0.007	Comparator: Not specified p=NS	NR	0=no dyspnea, 10=worst possible dyspnea.
Charles, 2008 <sup>34</sup> Opioids vs Opioids	Arm 2	Nebulized hydromorp hone	Breathlessne ss	VAS	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 5.29 (SD 1.92) Followup: Mean 3.39 (SD NR) Primary Followup: Mean 4.25 (Not reported 2.01)	Mean change from baseline: 1.04 (SD 1.38); SMD 0.75, (95% CI: 0.39 to 1.68), p<0.05	Comparator: Arm1 Difference in mean : 0.7 (95% CI: -0.51 to 1.03), p>0.4	NR	
	Arm 3	Systemic hydromorp hone	Breathlessne ss	VAS	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 5.28 (SD 2.01) Followup: Mean 3.53 (SD NR) Primary Followup: Mean 4.34 (Not reported 1.87)	Mean change from baseline: 0.94 (SD 1.49); SMD 0.63, (95% CI: 0.24 to 1.63), p<0.05	Comparator: Arm 2: SMD: -0.07 (95% CI: -0.69 to 0.55)  Comparator: Arm1 Difference in mean : 0.55 (95% CI: -0.45 to 0.77), p>0.4	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Gamborg, 2013 <sup>35</sup> Opioids vs Opioids	Arm 1	Red Morphine Drops	Dyspnea severity	VAS	Final: 1 hour	Baseline: 9 Followup: 9	Baseline: Mean 5.5 (SD 1.8) Followup: Mean 4.4 (SD 2.3)	NR	Ref SMD: -0.315 (95% CI: -1.202 to 0.572)	NR	p-value of treatment effect
	Arm 2	Subcutane ous Morphine	Dyspnea severity	VAS	Final: 1 hour	Baseline: 11 Followup: 11	Baseline: Mean 4.7 (SD 1.1) Followup: Mean 3 (SD 2)	NR	Comparator: Arm 1 p<0.0001	NR	p-value of treatment effect
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea intensity, beginning of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 0.6 (SD 0.8) Followup: Mean 0.7 (SD 1)	Mean change from baseline: 0.1 (SD 0.5), p=0.44	NR SMD: -0.29 (95% CI: -0.97 to 0.39)	NR	
	Arm 2	Low dose fentanyl	Dyspnea intensity, beginning of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 0.5 (SD 0.7) Followup: Mean 0.4 (SD 0.8)	Mean change from baseline: - 0.06 (SD 0.6), p=0.84	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea intensity, end of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 5.1 (SD 1.1) Followup: Mean 3.8 (SD 1.4)	Mean change from baseline: - 1.3 (SD 1.6), p=NR	NR SMD: 0.53 (95% CI: -0.15 to 1.22)	NR	
	Arm 2	Low dose fentanyl	Dyspnea intensity, end of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 5.1 (SD 2) Followup: Mean 4.5 (SD 2.1)	Mean change from baseline: - 0.5 (SD 1.4), p=NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea intensity, Difference between beginning and end of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 4.5 (SD 1.7) Followup: Mean 3.1 (SD 1.5)	Mean change from baseline: - 1.4 (SD 1.6), (95% CI: -2.4 to - 0.5), p=0.007	NR SMD: 0.56 (95% CI: -0.12 to 1.25)	NR	
	Arm 2	Low dose fentanyl	Dyspnea intensity, Difference between beginning and end of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 4.6 (SD 1.7) Followup: Mean 4.1 (SD 2.2)	Mean change from baseline: - 0.5 (SD 1.6), (95% CI: -1.3 to 0.3), p=0.24	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea intensity, Difference/dis tance walked (/100 m)	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 1.5 (SD 0.9) Followup: Mean 0.9 (SD 0.7)	Mean change from baseline: - 0.6 (SD 0.5), (95% CI: -0.9 to - 0.3), p<0.001	NR SMD: 0.6 (95% CI: -0.09 to 1.29)	NR	
	Arm 2	Low dose fentanyl	Dyspnea intensity, Difference/dis tance walked (/100 m)	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 1.6 (SD 0.9) Followup: Mean 1.3 (SD 0.7)	Mean change from baseline: - 0.3 (SD 0.5), (95% CI: -0.6 to - 0.1), p=0.03	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea intensity, Difference/min walked (/min)	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 0.8 (SD 0.3) Followup: Mean 0.5 (SD 0.3)	Mean change from baseline: - 0.3 (SD 0.3), (95% CI: -0.4 to - 0.1), p<0.001	NR SMD: 0.79 (95% CI: 0.09 to 1.50)	NR	
	Arm 2	Low dose fentanyl	Dyspnea intensity, Difference/min walked (/min)	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 0.8 (SD 0.3) Followup: Mean 0.7 (SD 0.4)	Mean change from baseline: - 0.1 (SD 0.2), (95% CI: -0.3 to - 0.008), p=0.05	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea unpleasantness, beginning of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 0.6 (SD 0.8) Followup: Mean 0.7 (SD 1.3)	Mean change from baseline: 0.1 (SD 0.7), p=0.94	NR SMD: -0.25 (95% CI: -0.93 to 0.43)	NR	
	Arm 2	Low dose fentanyl	Dyspnea unpleasantness, beginning of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 0.4 (SD 1) Followup: Mean 0.4 (SD 1)	Mean change from baseline: - 0.03 (SD 0.3), p=>0.99	N NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea unpleasantness, end of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 3.9 (SD 1.7) Followup: Mean 2.9 (SD 1.9)	Mean change from baseline: -1 (SD 1.9), p=NR	NR SMD: 0.19 (95% CI: -0.49 to 0.86)	NR	
	Arm 2	Low dose fentanyl	Dyspnea unpleasantness, end of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 4.1 (SD 2.4) Followup: Mean 3.4 (SD 2.8)	Mean change from baseline: - 0.7 (SD 1.3), p=NR	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea unpleasantness, Difference between beginning and end of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 3.3 (SD 2) Followup: Mean 2.2 (SD 1.8)	Mean change from baseline: -1 (SD 1.8), p=0.06	NR SMD: 0.25 (95% CI: -0.43 to 0.93)	NR	
	Arm 2	Low dose fentanyl	Dyspnea unpleasantness, Difference between beginning and end of walk	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 3.7 (SD 2.1) Followup: Mean 3 (SD 2.5)	Mean change from baseline: - 0.6 (SD 1.4), p=0.1	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea unpleasantne ss, Walk distance (m)	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 354.6 (SD 155.8) Followup: Mean 398.3 (SD 148.7)	Mean change from baseline: 43.7 (SD 30), (95% CI: 25.6 to 61.8), p=0.001	NR SMD: -0.59 (95% CI: -1.28 to 0.10)	NR	
	Arm 2	Low dose fentanyl	Dyspnea unpleasantne ss, Walk distance (m)	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 343.2 (SD 148.4) Followup: Mean 367.4 (SD 159.6)	Mean change from baseline: 24.2 (SD 35.7), (95% CI: 5.8 to 42.6), p=0.01	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dyspnea unpleasantne ss, Walk time (min)	Borg scale (modified)	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 6.2 (SD 1.9) Followup: Mean 6.7 (SD 1.7)	Mean change from baseline: 0.5 (SD 0.4), (95% CI: 0.3 to 0.7), p<0.001	NR SMD: -0.5 (95% CI: -1.18 to 0.18)	NR	
	Arm 2	Low dose fentanyl	Dyspnea unpleasantne ss, Walk time (min)	Borg scale (modified)	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 6 (SD 1.9) Followup: Mean 6.3 (SD 1.8)	Mean change from baseline: 0.3 (SD 0.4), (95% CI: 0.18 to 0.5), p=0.009	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hardy, 2016 <sup>36</sup> Anxiolytics vs Placebo	Arm 1	Placebo	Dyspnea	Dyspnea scoring scale (not specified, 0- 10)	Final: 60 minutes	Baseline: NR Followup: 115 (spray bottles)	Baseline: NR Followup: NR	Mean change from baseline: 2.1 (SD 2.2), p=NR	Ref	NR	N reported not as participants, but as spray bottles.
	Arm 2	Midazolam hydrochlori de	Dyspnea	Dyspnea scoring scale (not specified, 0- 10)	Final: 60 minutes	Baseline: NR Followup: 119 (spray bottles)	Baseline: NR Followup: NR	Mean change from baseline: 2.2 (SD 2.2), p=NR	Comparator: Arm1 p=0.753	NR	N reported not as participants, but as spray bottles.
Peoples, 2016 <sup>45</sup> Anxiolytics vs Placebo	Arm 1	Placebo	Dyspnea severity, complete case	Oxygen Cost Diagram (OCD)	Final: 28 days	Baseline: 192 Followup: 155	Baseline: Mean 8.4 (SD 2.6) Followup: Mean 9.3 (SD NR)	NR	Ref	Clinic site	Complete case only
	Arm 2	Buspirone	Dyspnea severity, complete case	Oxygen Cost Diagram (OCD)	Final: 28 days	Baseline: 187 Followup: 156	Baseline: Mean 8.7 (SD 2.6) Followup: Mean 9 (SD NR)	NR	Comparator: Arm 1 Estimate, not specified: -0.52 (SE 0.27) (95% CI: -1.045 to 0.005), p=0.052	Clinic site	Complete case only



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Peoples, 2016 <sup>45</sup> Anxiolytics vs Placebo	Arm 1	Placebo	Dyspnea severity, multiple imputation estimate	Oxygen Cost Diagram (OCD)	Final: 28 days	Baseline: 192 Followup: 192	Baseline: Mean 8.4 (SD 2.6) Followup: NR	NR	Ref	Clinic site	Multiple imputation only
	Arm 2	Buspirone	Dyspnea severity, multiple imputation estimate	Oxygen Cost Diagram (OCD)	Final: 28 days	Baseline: 187 Followup: 187	Baseline: Mean 8.7 (SD 2.6) Followup: NR	NR	Comparator: Arm 1 Estimate, not specified: -0.48 (SE 0.27) (95% CI: -1.020 to 0.058), p=0.08	Clinic site	Multiple imputation only



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Simon, 2016 <sup>47</sup> Anxiolytics vs Placebo	Arm 1	Immediate release morphine	Breathlessne ss intensity	NRS	Final: 30 minutes Primary: 10 minutes	Baseline: 10 Final: 6 Primary: 6	Baseline: Mean 6 (SD 2.2) Final: NR Primary: NR	Mean change from baseline Last followup: 3.1 (SD 2.0) Primary followup: 1.7 (SD 1.4) p=NR	Ref	NR	
	Arm 2	Fentanyl buccal tablet	Breathlessne ss intensity	NRS	Final: 30 minutes Primary: 10 minutes	Baseline: 10 Final: 6 Primary: 6	Baseline: Mean 6 (SD 2.2) Final: NR Primary: NR	Mean change from baseline Last followup: 4.0 (SD 2.1) Primary followup: 2.8 (SD 2.0) p=NR	Comparator: Arm 1 Difference in mean Last followup: 1.0 (95% CI: -0.9 to 2.8), p=0.234 Primary followup: 1.1 (95% CI: -0.0 to 2.2), p=0.051 p=NR SMD: 0.44 (95% CI: -0.45 to 1.33)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Simon, 2016 <sup>47</sup> Anxiolytics vs Placebo	Arm 1	Immediate release morphine	Sum of Breathlessness intensity difference (SBID)	NR	Final: 60 minutes Primary: 15 minutes	Baseline: 10 Final: 6 Primary: 6	Baseline: Mean NR (Not reported NR) Final: NR Primary: NR	Mean change from baseline Last followup: 2.7 (SD 1.6) Primary followup: 1.3 (SD 1.1) p=NR	Ref	NR	
	Arm 2	Fentanyl buccal tablet	Sum of Breathlessness intensity difference (SBID)	NR	Final: 60 minutes Primary: 15 minutes	Baseline: 10 Final: 6 Primary: 6	Baseline: Mean NR (Not reported NR) Final: NR Primary: NR	Mean change from baseline Last followup: 3.9 (SD 1.9) Primary followup: 2.3 (SD 1.6) p=NR	Comparator: Arm 1 Difference in mean Last followup: 1.1 (95% CI: -0.2 to 2.5), p=0.089 Primary followup: 1.0 (95% CI: 0.0 to 2.0), p=0.047 p=NR SMD: 0.68 (95% CI: -0.22 to 1.59)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Simon, 2016 <sup>47</sup> Anxiolytics vs Placebo	Arm 1	Immediate release morphine	Decline of breathlessnes s intensity	NR	Final: 60 minutes Primary: 10 minutes	Baseline: 10 Final: 6 Primary: 6	Baseline: Mean NR (Not reported NR) Final: NR Primary: NR	Mean change from baseline Last followup: 0.1 (SD 0.0) Primary followup: - 0.2 (SD 0.1) p=NR	Ref	NR	
	Arm 2	Fentanyl buccal tablet	Decline of breathlessnes s intensity	NR	Final: 60 minutes Primary: 10 minutes	Baseline: 10 Final: 6 Primary: 6	Baseline: Mean NR (Not reported NR) Final: NR Primary: NR	Mean change from baseline Last followup: - 0.1 (SD 0.0) Primary followup: - 0.3 (SD 0.1) p=NR	Comparator: Arm 1 Difference in mean Last followup: - 0.0 (95% CI: -0.0 to 0.0), p=0.659 Primary followup: -0.1 (95% CI: - 0.2 to 0.0), p=0.057 p=NR SMD: -1 (95% CI: -1.94 to - 0.06)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Dyspnea, ESAS (average 24hr)	ESAS Dyspnea	Final: 14 days Primary: 7 days	Baseline: 19 Followup: 15 Primary FU: 14	Baseline: Mean 4.7 (SD 1.5) Followup: Mean 2.9 (SD 1.5) Primary Followup: Mean 3.3 (SD 2.1)	Mean change from baseline: - 1.7 (SD NR), (95% CI: -2.7 to - 0.7), p=0.004	Ref SMD: -0.22 (95% CI: -0.86 to 0.42)	NR	14 day estimates include a 7 day open label period
	Arm 2	Dexamethasone	Dyspnea, ESAS (average 24hr)	ESAS Dyspnea	Final: 14 days Primary: 7 days	Baseline: 19 Followup: 13 Primary FU: 16	Baseline: Mean 5 (SD 2.1) Followup: Mean 3.2 (SD 2.1) Primary Followup: Mean 3.6 (SD 2.6)	Mean change from baseline: - 2.1 (SD NR), (95% CI: -3.5 to - 0.6), p=0.01	Comparator: Arm 1 Difference in mean : -0.4 (95% CI: -2 to 1.2), p=NS	NR	14 day estimates include a 7 day open label period



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Dyspnea, now	Modified Dyspnea Borg Scale	Final: 14 days Primary: 7 days	Baseline: 19 Followup: 14 Primary FU: 17	Baseline: Mean 4.6 (SD 1.6) Followup: Mean 3 (SD 1.8) Primary Followup: Mean 4.2 (SD 2.4)	Mean change from baseline: - 1.5 (SD NR), (95% CI: -2.5 to - 0.5), p=Significa nt	Ref SMD: -0.06 (95% CI: -0.70 to 0.58)	NR	14 day estimates include a 7 day open label period
	Arm 2	Dexamethasone	Dyspnea, now	Modified Dyspnea Borg Scale	Final: 14 days Primary: 7 days	Baseline: 19 Followup: 12 Primary FU: 18	Baseline: Mean 4.2 (SD 1.7) Followup: Mean 2.6 (SD 1.5) Primary Followup: Mean 3.1 (SD 2.2)	Mean change from baseline: - 1.6 (SD NR), (95% CI: -3 to - 0.2), p=Significa nt	Comparator: Arm 1 Difference in mean : -0.1 (95% CI: -1.6 to 1.4), p=NS	NR	14 day estimates include a 7 day open label period



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 1993 <sup>32</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea intensity	VAS	Final: 60 minutes	Baseline: 10 Final: 10	Baseline: Mean 31 (SD 27) Final: Mean 35 (SD 29)	NR	Ref	NR	
	Arm 2	Morphine	Dyspnea intensity	VAS	Final: 60 minutes	Baseline: 10 Final: 10	Baseline: Mean 30 (SD 23) Final: Mean 16 (SD 18)	NR	Comparator: Arm1 Difference in mean: NR Baseline difference between arms: p >0.2; Followup difference between arms: p <0.01 SMD: -0.73 (95% CI: -1.64 to 0.18)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Charles, 2008 <sup>34</sup> Opioids vs Placebo	Arm 1	Nebulized saline	Breathlessn ess	VAS	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 5.59 (SD 2.34) Followup: Mean 3.74 (SD NR) Primary Followup: Mean 4.81 (NR 1.78)	Mean change from baseline (follow up 10 minutes); 0.78; SMD 0.50 (SD 1.54), (95% CI: 0.05 to 1.50), p<0.05	Ref Primary FU: SMD: 0.17 (95% CI: -0.44 to 0.80)	NR	Follow-up data at 1 hour taken from figures
	Arm 2	Nebulized hydromorphone	Breathlessn ess	VAS	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 5.29 (SD 1.92) Followup: Mean 3.39 (SD NR) Primary Followup: Mean 4.25 (NR 2.01)	Mean change from baseline: 1.04; SMD 0.75 (SD 1.38), (95% CI: 0.39 to 1.68), p<0.05	Comparator: Arm1 Difference in mean : 0.7 (95% CI: -0.51 to 1.03), p>0.4	NR	Follow-up data at 1 hour taken from figures



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Charles, 2008 <sup>34</sup> Opioids vs Placebo	Arm 1	Nebulized saline	Breathlessn ess	VAS	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 5.59 (SD 2.34) Followup: Mean 3.74 (SD NR) Primary Followup: Mean 4.81 (NR 1.78)	Mean change from baseline: 0.78; SMD 0.50 (SD 1.54), (95% CI: 0.05 to 1.50), p<0.05	Ref Primary FU: SMD: 0.11 (95% CI: - 0.51 to 0.73)	NR	Follow-up data at 1 hour taken from figures
	Arm 2	Nebulized hydromorphone	Breathlessn ess	VAS	Final: NR	Baseline: NR Followup: NR	Baseline: NR Followup: NR	NR	Comparator: Arm3 Difference in mean : 0.45 (95% CI: - 0.37 to 0.57), p>0.4	NR	Difference between treatments in rapid improvement
	Arm 3	Systemic hydromorphone	Breathlessn ess	VAS	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 5.28 (SD 2.01) Followup: Mean 3.53 (SD NR) Primary Followup: Mean 4.34 (NR 1.87)	Mean change from baseline: 0.94; SMD 0.63 (SD 1.49), (95% CI: 0.24 to 1.63), p<0.05	Comparator: Arm1 Difference in mean : 0.55 (95% CI: - 0.45 to 0.77), p>0.4	NR	Follow-up data at 1 hour taken from figures
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea intensity, 0 minutes	Numeric Rating Scale	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 2.9 (SD 2.7) Followup: Mean 2.2 (SD 2.1)	Mean change from baseline: - 0.7 (SD NR), (95% CI: -1.5 to 0.1), p=NS	SMD: -0.11 (95% CI: - 0.98to 0.77)	NR	
	Arm 2	Fentanyl	Dyspnea intensity, 0 minutes	Numeric Rating Scale	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 1.5 (SD 1.1) Followup: Mean 0.6 (SD 1.1)	Mean change from baseline: - 0.9 (SD NR), (95% CI: -1.8 to - 0.04), p=Significant	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea intensity, 6 minutes	Numeric Rating Scale	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 7.1 (SD 2.8) Followup: Mean 5.1 (SD 2.9)	Mean change from baseline: -2 (SD NR), (95% CI: -4 to 0.02), p=NS	SMD: 0.09 (95% CI: - 0.79to 0.97)	NR	
	Arm 2	Fentanyl	Dyspnea intensity, 6 minutes	Numeric Rating Scale	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 5.4 (SD 1.3) Followup: Mean 3.6 (SD 1.3)	Mean change from baseline: - 1.8 (SD NR), (95% CI: -3.2 to - 0.4), p=Significant	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea rating	Dyspnea numeric rating scale, at 0 minutes (before 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 1.7 (SD 1.2) Followup: Mean 1.2 (SD 1.4)	Mean change from baseline: - 0.5 (SD NR), (95% CI: -1.3 to 0.3), p=NS	SMD: -0.26 (95% CI: - 1.06 to 0.55)	NR	
	Arm 2	FPNS	Dyspnea rating	Dyspnea numeric rating scale, at 0 minutes (before 6 MWT)	Final: Second Walk, 15 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 2.4 (SD 1.7) Followup: Mean 1.5 (SD 1.8)	Mean change from baseline: - 0.9 (SD NR), (95% CI: -1.7 to - 0.1), p=Significant	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea rating	Dyspnea numeric rating scale, at 0 minutes (before 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 1.7 (SD 1.2) Followup: Mean 1.1 (SD 1.3)	Mean change from baseline: - 0.5 (SD NR), (95% CI: -1.4 to 0.3), p=NS	SMD: -0.40 (95% CI: - 1.21 to 0.41)	NR	
	Arm 2	FPNS	Dyspnea rating	Dyspnea numeric rating scale, at 0 minutes (before 6 MWT)	Final: Third Walk, same day, 15 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 2.4 (SD 1.7) Followup: Mean 1.2 (SD 1.7)	Mean change from baseline: - 1.3 (SD NR), (95% CI: -2.0 to - 0.5), p=Significant	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea rating	Dyspnea numeric rating scale, at 6 minutes (after 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 5.4 (SD 2) Followup: Mean 3.8 (SD 2.7)	Mean change from baseline: - 1.7 (SD NR), (95% CI: -3.3 to - 0.1), p=Significant	SMD: -0.21 (95% CI: - 1.01 to 0.59)	NR	
	Arm 2	FPNS	Dyspnea rating	Dyspnea numeric rating scale, at 6 minutes (after 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 6.2 (SD 1.9) Followup: Mean 4.1 (SD 2.6)	Mean change from baseline: -2 (SD NR), (95% CI: -3.5 to -0.6), p=Significant	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea rating	Dyspnea numeric rating scale, at 6 minutes (after 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 5.4 (SD 2) Followup: Mean 2.8 (SD 2.5)	Mean change from baseline: - 2.5 (SD NR), (95% CI: -4.2 to - 0.9), p=Significant	SMD: 0.09(95% CI: -0.71 to 0.89)	NR	
	Arm 2	FPNS	Dyspnea rating	Dyspnea numeric rating scale, at 6 minutes (after 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 6.2 (SD 1.9) Followup: Mean 3.8 (SD 2.6)	Mean change from baseline: - 2.3 (SD NR), (95% CI: -4.0 to - 0.7), p=Significant	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea rating	Dyspnea Borg Scale, at 0 minutes (before 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 1.3 (SD 1) Followup: Mean 0.8 (SD 1.2)	Mean change from baseline: - 0.4 (SD NR), (95% CI: -1.0 to 0.1), p=NS	Ref SMD: -0.24 (95% CI: - 1.04 to 0.57)	NR	
	Arm 2	FPNS	Dyspnea rating	Dyspnea Borg Scale, at 0 minutes (before 6 MWT)	Final: Second Walk, 15 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 2 (SD 1.3) Followup: Mean 1.2 (SD 1.5)	Mean change from baseline: - 0.8 (SD NR), (95% CI: -1.6 to - 0.1), p=Significant	Comparator: Arm 1 p=NS	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea rating	Dyspnea Borg Scale, at 0 minutes (before 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 1.3 (SD 1) Followup: Mean 1 (SD 1.3)	Mean change from baseline: - 0.2 (SD NR), (95% CI: -0.9 to 0.5), p=NS	Ref SMD: -0.52 (95% CI: - 1.344 to 0.29)	NR	
	Arm 2	FPNS	Dyspnea rating	Dyspnea Borg Scale, at 0 minutes (before 6 MWT)	Final: Third Walk, same day, 15 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 2 (SD 1.3) Followup: Mean 1 (SD 1.6)	Mean change from baseline: -1 (SD NR), (95% CI: -1.9 to -0.2), p=Significant	Comparator: Arm 1 p=NS	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea rating	Dyspnea Borg Scale, at 6 minutes (after 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 4.4 (SD 1.8) Followup: Mean 2.7 (SD 2.5)	Mean change from baseline: - 1.7 (SD NR), (95% CI: -3.3 to - 0.1), p=Significant	Ref SMD: 0 (95% CI: -0.809 to 0.80)	NR	
	Arm 2	FPNS	Dyspnea rating	Dyspnea Borg Scale, at 6 minutes (after 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 5 (SD 2) Followup: Mean 3.3 (SD 2.3)	Mean change from baseline: - 1.8 (SD NR), (95% CI: -3.1 to - 0.4), p=Significant	Comparator: Arm 1 p=NS	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea rating	Dyspnea Borg Scale, at 6 minutes (after 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 4.4 (SD 1.8) Followup: Mean 2.3 (SD 2.2)	Mean change from baseline: - 2.4 (SD NR), (95% CI: -4.2 to - 0.6), p=Significant	Ref SMD: 0.09 (95% CI: - 0.71 to 0.89)	NR	
	Arm 2	FPNS	Dyspnea rating	Dyspnea Borg Scale, at 6 minutes (after 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 5 (SD 2) Followup: Mean 3.1 (SD 2.9)	Mean change from baseline: - 1.7 (SD NR), (95% CI: -3.5 to 0), p=Significant	Comparator: Arm 1 p=NS	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea, at 0 minutes (before walk)	NRS	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 1 (SD 1.2) Followup: Mean 1 (SD 0.9)	Mean change from baseline: 0 (SD NR), (95% CI: -0.7 to 0.6), p=NS	NR SMD: -0.086 (95% CI: - 0.97 to 0.80)	NR	
	Arm 2	FBT	Dyspnea, at 0 minutes (before walk)	NRS	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 0.9 (SD 1.4) Followup: Mean 0.8 (SD 1)	Mean change from baseline: - 0.1 (SD NR), (95% CI: -0.7 to 0.5), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea, at 6 minutes (after walk)	NRS	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 6 (SD 1.8) Followup: Mean 4.8 (SD 2.2)	Mean change from baseline: - 1.2 (SD NR), (95% CI: -2.5 to 0.1), p=NS	NR SMD: -0.67 (95% CI: - 1.58 to 0.24)	NR	
	Arm 2	FBT	Dyspnea, at 6 minutes (after walk)	NRS	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 5.4 (SD 2.1) Followup: Mean 2.9 (SD 1.2)	Mean change from baseline: - 2.6 (SD NR), (95% CI: -3.9 to - 1.2), p=Significant	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea, difference between 0- 6 minutes	NRS	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 5 (SD 1.9) Followup: Mean 3.9 (SD 2.4)	Mean change from baseline: - 1.1 (SD NR), (95% CI: -2.5 to 0.2), p=NS	NR SMD: -0.73 (95% CI: - 1.65 to 0.18)	NR	
	Arm 2	FBT	Dyspnea, difference between 0- 6 minutes	NRS	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 4.6 (SD 1.7) Followup: Mean 2.1 (SD 0.9)	Mean change from baseline: - 2.4 (SD NR), (95% CI: -3.5 to - 1.3), p=Significant	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea, at 0 minutes (before walk)	Borg	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 1 (SD 1.1) Followup: Mean 0.8 (SD 1.4)	Mean change from baseline: - 0.2 (SD NR), (95% CI: -0.9 to 0.6), p=NS	NR SMD: 0.08 (95% CI: - 0.80 to 0.96)	NR	
	Arm 2	FBT	Dyspnea, at 0 minutes (before walk)	Borg	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 0.8 (SD 1.4) Followup: Mean 0.7 (SD 0.8)	Mean change from baseline: - 0.1 (SD NR), (95% CI: -0.7 to 0.6), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea, at 6 minutes (after walk)	Borg	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 4.5 (SD 1.7) Followup: Mean 3.8 (SD 2)	Mean change from baseline: - 0.7 (SD NR), (95% CI: -1.9 to 0.5), p=NS	NR SMD: -0.59 (95% CI: - 1.49 to 0.31)	NR	
	Arm 2	FBT	Dyspnea, at 6 minutes (after walk)	Borg	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 4.1 (SD 1.6) Followup: Mean 2.4 (SD 1.2)	Mean change from baseline: - 1.7 (SD NR), (95% CI: -2.6 to - 0.7), p=Significant	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea, difference between 0- 6 minutes	Borg	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 3.5 (SD 1.7) Followup: Mean 3 (SD 1.5)	Mean change from baseline: - 0.5 (SD NR), (95% CI: -1.9 to 0.8), p=NS	NR SMD: -0.68 (95% CI: - 1.59 to 0.23)	NR	
	Arm 2	FBT	Dyspnea, difference between 0- 6 minutes	Borg	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 3.3 (SD 1.8) Followup: Mean 1.7 (SD 1.3)	Mean change from baseline: - 1.6 (SD NR), (95% CI: -2.9 to - 0.3), p=Significant	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Pinna, 2015 <sup>46</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea	Numeric Rating Scale	Final: 60 minutes Primary: Right after end of walk	Baseline: 11 Followup: 11 Primary FU: 11	Baseline: Mean 6 (SD 1.6), Range: 4 to 9 Followup: Mean 2.6 (SD 2.2), Range: 0 to 6 Primary Followup: Mean 5.5 (SD 2.8), Range: 1 to 8	NR	Ref SMD: 0.20 (95% CI: - 0.63 to 1.04)	Period effect	Baseline before walk
	Arm 2	Fentanyl citrate	Dyspnea	Numeric Rating Scale	Final: 60 minutes Primary: Right after end of walk	Baseline: 11 Followup: 11 Primary FU: 11	Baseline: Mean 5.4 (SD 2), Range: 2 to 9 Followup: Mean 2.4 (SD 1.9), Range: 0 to 6 Primary Followup: Mean 4.5 (SD 2), Range: 0 to 7	NR	Comparator: Arm1 Baseline: p=0.477; Followup: p=0.563; Primary FU: p=0.297	Period effect	Baseline before walk
Pinna, 2015 <sup>46</sup> Opioids vs Placebo	Arm 1	Placebo	Dyspnea	Numeric Rating Scale	Final: 60 minutes Primary: Right after end of walk	Baseline: 11 Followup: 11 Primary FU: 11	Baseline: Median 6 (SD NR), Range: Q1/Q3: 5.0/7.0 Followup: Median 3 (SD NR), Range: Q1/Q3: 0 to 4 Primary Followup: Median 6 (SD NR), Range: Q1/Q3: 1/8	NR	Ref	Period effect	Baseline before walk, recorded mean and median as separate outcomes to fit form
	Arm 2	Fentanyl citrate	Dyspnea	Numeric Rating Scale	Final: 60 minutes Primary: Right after end of walk	Baseline: 11 Followup: 11 Primary FU: 11	Baseline: Median 5 (SD NR), Range: Q1/Q3: 4.0/7.0 Followup: Median 2 (SD NR), Range: Q1/Q3: 0 to 4 Primary Followup: Median 5 (SD NR), Range: Q1/Q3: 0/7	NR	Comparator: Arm1 Baseline: p=0.477; Followup: p=0.297; Primary FU: p=0.563	Period effect	Baseline before walk, recorded mean and median as separate outcomes to fit form

6MWT=6 minute walk test; BTD=breakthrough dyspnea; CI=confidence interval; FPNS= fentanyl pectin nasal spray; FU=follow-up; IQR=interquartile range; N=sample size; NR=not reported; NRS=numerical rating system; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SE=standard error; SMD=standardized mean difference; VAS=Visual Analogue Scale



Evidence Table D-42. Breathlessness categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Anxiolytics vs Combination	Arm 2	Midazolam	Patients with breakthrough dyspnea	NR	Final: 48 hours	Followup: 23	Final FU: 9/23 (38.5)	p=NR	Comparator: NR p=NS RR: 0.56 (95% CI: 0.22 to 1.41)	NR	
	Arm 3	Morphine+ Midazolam	Patients with breakthrough dyspnea	NR	Final: 48 hours	Followup: 23	Final FU: 5/23 (24)	p=NR	Comparator: NR p=NS	NR	
Navigante, 2006 <sup>43</sup> Anxiolytics vs Combination	Arm 2	Midazolam	Patients who experienced dyspnea relief	Borg scale	Final: 24 hours	Followup: 26	Final FU: 12/26 (46)	p=NR	Comparator: Arm3 p=0.004 RR: 1.99 (95% CI: 1.30 to 3.07)	NR	Arm 2 is either 0.0004 or 0.004 (different in the text vs the figure legend)
	Arm 3	Morphine+ Midazolam	Patients who experienced dyspnea relief	Borg scale	Final: 24 hours	Followup: 25	Final FU: 23/25 (92)	p=NR	Ref	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Dyspnea therapeutic failure, NRS≥8	Numeric Rating Scale	Final: 5 days	Followup: 30	Final FU: 6/30 (30)	p=NR	NR RR: 0.07 (95% CI: 0.004 to 1.27)	NR	
	Arm 2	Midazolam	Dyspnea therapeutic failure, NRS≥8	Numeric Rating Scale	Final: 5 days	Followup: 31	Final FU: 0/31 (0)	p=NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Patients with ≥1 BTD episode	Numeric Rating Scale	Final: 60 minutes; Primary: 5 days	Followup: 30 Primary FU: 30	Final FU: 25/30 (83.3); Primary: 21/30 (70)	p=0.48	Ref RR: 0.97 (95% CI: 0.76 to 1.22)	NR	All data except p- values taken from figure,
	Arm 2	Midazolam	Patients with ≥1 BTD episode	Numeric Rating Scale	Final: 60 minutes; Primary: 5 days	Followup: 31 Primary FU: 31	Final FU: 25/31 (80.6); Primary: 13/31 (41.9)	p=0.002	Comparator: Arm1 p≤0.001	NR	All data except p- values taken from figure,
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Patients who experienced no dyspnea relief	Borg scale	Final: 24 hours	Followup: 29	Final FU: 9/29 (31)	NR	NR RR: 1.62 (95% CI: 0.93 to 2.83)	NR	EPC team calculated inverse of patients with dyspnea relief for analysis
	Arm 2	Midazolam	Patients who experienced no dyspnea relief	Borg scale	Final: 24 hours	Followup: 26	Final FU: 14/26 (54)	NR	NA	NR	EPC team calculated inverse of patients with dyspnea relief for analysis
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Patients who experienced dyspnea relief	Borg scale	Final: 24 hours	Followup: 29	Final FU: 20/29 (69)	p=NR	Comparator: Arm3 p=0.03 RR: 0.67 (95% CI: 0.41 to 1.08)	NR	
	Arm 2	Midazolam	Patients who experienced dyspnea relief	Borg scale	Final: 24 hours	Followup: 26	Final FU: 12/26 (46)	p=NR	Comparator: Arm3 p=0.004	NR	Arm 2 is either 0.0004 or 0.004 (different in the text vs the figure legend)



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Patients with breakthrough dyspnea	NR	Final: 48 hours	Followup: 24	Final FU: 9/24 (38)	p=NR	Comparator: NR p=NS RR: 1.04 (95% CI: 0.51 to 2.16)	NR	
	Arm 2	Midazolam	Patients with breakthrough dyspnea	NR	Final: 48 hours	Followup: 23	Final FU: 9/23 (38.5)	p=NR	Comparator: NR p=NS	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Combination	Arm 1	Morphine	Patients with breakthrough dyspnea	NR	Final: 48 hours	Followup: 24	Final FU: 9/24 (38)	p=NR	Comparator: NR p=NS RR: 0.58 (95% CI: 0.23 to 1.47)	NR	
	Arm 3	Morphine+ Midazolam	Patients with breakthrough dyspnea	NR	Final: 48 hours	Followup: 23	Final FU: 5/23 (24)	p=NR	Comparator: NR p=NS	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Combination	Arm 1	Morphine	Patients who experienced dyspnea relief	Borg scale	Final: 24 hours	Followup: 29	Final FU: 20/29 (69)	p=NR	Comparator: Arm3 p=0.03 RR: 1.33 (95% CI: 1.02 to 1.75)	NR	
	Arm 3	Morphine+ Midazolam	Patients who experienced dyspnea relief	Borg scale	Final: 24 hours	Followup: 25	Final FU: 23/25 (92)	p=NR	Ref	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Tian, 2016 <sup>48</sup> Corticosteroids vs Bronchodilators	Arm 2	Methylpred nisolone	Dyspnea VAS score reduced 50%	VAS	Final: 1 hour	Followup: 111	Final FU: 69/111 (62.16)	p=NR	Comparator: Arm1 Chi-squared: 17.826, p=0.000 RR: 0.79 (95% CI: 0.62 to 1.001)	NR	
	Arm 3	Aminophylli ne	Dyspnea VAS score reduced 50%	VAS	Final: 1 hour	Followup: 114	Final FU: 56/114 (49.12)	p=NR	Comparator: Arm1 Chi-squared: 37.172, p=0.000	NR	
Tian, 2016 <sup>48</sup> Opioids vs Corticosteroids	Arm 1	Morphine	Dyspnea VAS score reduced 50%	VAS	Final: 1 hour	Followup: 118	Final FU: 102/118 (86.44)	p=NR	Ref RR: 0.72 (95% CI: 0.61 to 0.85)	NR	
	Arm 2	Methylpred nisolone	Dyspnea VAS score reduced 50%	VAS	Final: 1 hour	Followup: 111	Final FU: 69/111 (62.16)	p=NR	Comparator: Arm1 Chi-squared: 17.826, p=0.000	NR	
Tian, 2016 <sup>48</sup> Opioids vs Bronchodilators	Arm 1	Morphine	Dyspnea VAS score reduced 50%	VAS	Final: 1 hour	Followup: 118	Final FU: 102/118 (86.44)	p=NR	Ref RR: 0.57 (95% CI: 0.47 to 0.69)	NR	
	Arm 3	Aminophylli ne	Dyspnea VAS score reduced 50%	VAS	Final: 1 hour	Followup: 114	Final FU: 56/114 (49.12)	p=NR	Comparator: Arm1 Chi-squared: 37.172, p=0.000	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Patients reported dyspnea was at least "somewhat better"	NR	Final: After second walk	Followup: 13	Final FU: 8/13 (64)	p=NR	NR RR: 0.38 (95% CI: 0.15 to 1.00)	NR	
	Arm 2	Low dose fentanyl	Patients reported dyspnea was at least "somewhat better"	NR	Final: After second walk	Followup: 17	Final FU: 4/17 (24)	p=NR	NA	NR	
Hardy, 2016 <sup>36</sup> Anxiolytics vs Placebo	Arm 1	Placebo	Dyspnea	Dyspnea scoring scale (not specified, 0-10)	Final: 60 minutes	Followup: 115 (spray bottles)	Final FU: 59/115 (spray bottles) (51.3)	p=NR	Ref RR: 1.10 (95% CI: 0.86 to 1.39)	NR	
	Arm 2	Midazolam hydrochlori de	Dyspnea	Dyspnea scoring scale (not specified, 0-10)	Final: 60 minutes	Followup: 119 (spray bottles)	Final FU: 67/119 (spray bottles) (56.3)	p=NR	Comparator: Arm1 p=0.443	NR	

BTD=breakthrough dyspnea; CI=confidence interval; FU=follow-up; N=sample size; NR=not reported; NRS=numerical rating scale; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation; SE=standard error; VAS=Visual Analogue Scale



**Evidence Table D-43. Quality of life continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Dyspnea	EORTC QLQ-C30 Dyspnea (past week)	Final: 14 days Primary: 7 days	Baseline: 19 Followup: 15 Primary FU: 13	Baseline: Mean 49.1 (SD 20.4) Followup: Mean 40 (SD 18.7) Primary Followup: Mean 43.6 (SD 16)	Mean change from baseline: -6.7 (SD NR), (95% CI: -19.2 to 5.8), p=NS	Ref SMD: -0.12 (95% CI: -0.86 to 0.62)	NR	14 day estimates include a 7 day open label period
	Arm 2	Dexametha sone	Dyspnea	EORTC QLQ-C30 Dyspnea (past week)	Final: 14 days Primary: 7 days	Baseline: 19 Followup: 13 Primary FU: 16	Baseline: Mean 57.9 (SD 29.1) Followup: Mean 46.1 (SD 16.9) Primary Followup: Mean 47.9 (SD 17.1)	Mean change from baseline: -7.7 (SD NR), (95% CI: -22.3 to 6.9), p=NS	Comparator: Arm 1 Difference in mean : -1 (95% CI: -18.4 to 16.4), p=NS	NR	14 day estimates include a 7 day open label period

CI=confidence interval; EORTC QLQ-C30= European Organization for Research and Treatment Quality of Life Questionnaire; FU=followup; N=sample size; NR=not reported; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-44. Blood pressure continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Systolic blood pressure, beginning of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 130.9 (SD 19.4) Followup: Mean 127.2 (SD 18.3)	Mean change from baseline: -3.6 (SD 15), p=0.48	NR SMD: -0.06 (95% CI: -0.73to 0.62)	NR	
	Arm 2	Low dose fentanyl	Systolic blood pressure, beginning of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 121.8 (SD 18.7) Followup: Mean 117.5 (SD 16.9)	Mean change from baseline: -4.4 (SD 12.7), p=0.2	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Systolic blood pressure, end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 142.4 (SD 15.9) Followup: Mean 145.7 (SD 14.6)	Mean change from baseline: 3.3 (SD 10.1), p=NR	NR SMD: 0.15 (95% CI: -0.53 to 0.82)	NR	
	Arm 2	Low dose fentanyl	Systolic blood pressure, end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 131.4 (SD 13.7) Followup: Mean 136.3 (SD 14.1)	Mean change from baseline: 4.9 (SD 11.4), p=NR	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Systolic blood pressure, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 11.5 (SD 12.7) Followup: Mean 18.5 (SD 9.3)	Mean change from baseline: 6.9 (SD 13.7), p=0.1	NR SMD: 0.14 (95% CI: -0.54 to 0.81)	NR	
	Arm 2	Low dose fentanyl	Systolic blood pressure, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 9.5 (SD 18.2) Followup: Mean 18.8 (SD 14.1)	Mean change from baseline: 9.3 (SD 20), p=0.1	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Diastolic blood pressure, beginning of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 76.6 (SD 11.7) Followup: Mean 77.7 (SD 6.8)	Mean change from baseline: 1.1 (SD 7), p=0.62	NR SMD: 0.17 (95% CI: -0.51 to 0.84)	NR	
	Arm 2	Low dose fentanyl	Diastolic blood pressure, beginning of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 71.8 (SD 10.6) Followup: Mean 73.9 (SD 11)	Mean change from baseline: 2.2 (SD 6), p=0.17	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Diastolic blood pressure, end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 81.5 (SD 8.6) Followup: Mean 85.9 (SD 6.5)	Mean change from baseline: 4.4 (SD 6.1), p=NR	NR SMD: -0.21 (95% CI: -0.88 to 0.47)	NR	
	Arm 2	Low dose fentanyl	Diastolic blood pressure, end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 75.4 (SD 10.7) Followup: Mean 78.2 (SD 13.3)	Mean change from baseline: 2.8 (SD 9), p=NR	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Diastolic blood pressure, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 4.9 (SD 7.1) Followup: Mean 8.2 (SD 7.1)	Mean change from baseline: 3.3 (SD 6.7), p=0.11	NR SMD: -0.30 (95% CI: -0.98 to 0.38)	NR	
	Arm 2	Low dose fentanyl	Diastolic blood pressure, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 3.6 (SD 8.8) Followup: Mean 4.2 (SD 7.4)	Mean change from baseline: 0.7 (SD 10.1), p=0.44	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Diastolic blood pressure, at 0 minutes (before walk)	NR	Final: Second walk, not specified	Baseline: 11 Followup: 11	Baseline: Mean 71 (SD 7.4) Followup: Mean 76.2 (SD 12.1)	Mean change from baseline: 5.2, (95% CI: 0.5 to 9.8), p=Significant	NR SMD: -0.49 (95% CI: -1.39to 0.40)	NR	
	Arm 2	FBT	Diastolic blood pressure, at 0 minutes (before walk)	NR	Final: Second walk, not specified	Baseline: 9 Followup: 9	Baseline: Mean 77.1 (SD 10.2) Followup: Mean 77.3 (SD 9.1)	Mean change from baseline: 0.2, (95% CI: -2.7 to 3.1), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Diastolic blood pressure, at 6 minutes (after walk)	NR	Final: Second walk, not specified	Baseline: 11 Followup: 11	Baseline: Mean 78.4 (SD 8.8) Followup: Mean 77.5 (SD 12.3)	Mean change from baseline: -0.8, (95% CI: -5.7 to 4.1), p=NS	NR SMD: -0.16 (95% CI: -1.04 to 0.73)	NR	
	Arm 2	FBT	Diastolic blood pressure, at 6 minutes (after walk)	NR	Final: Second walk, not specified	Baseline: 9 Followup: 9	Baseline: Mean 77.9 (SD 9.8) Followup: Mean 75.4 (SD 8.4)	Mean change from baseline: -2.4, (95% CI: -6.8 to 1.9), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Diastolic blood pressure, difference between 0-6 minutes	NR	Final: Second walk, not specified	Baseline: 11 Followup: 11	Baseline: Mean 7.4 (SD 7.3) Followup: Mean 1.4 (SD 5.3)	Mean change from baseline: -6, (95% CI: -11.7 to -0.3), p=NS	NR SMD: 0.59 (95% CI: -0.32 to 1.49)	NR	
	Arm 2	FBT	Diastolic blood pressure, difference between 0-6 minutes	NR	Final: Second walk, not specified	Baseline: 9 Followup: 9	Baseline: Mean 0.8 (SD 2.9) Followup: Mean -1.9 (SD 4.9)	Mean change from baseline: -2.7, (95% CI: -7 to 1.7), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Systolic blood pressure, at 0 minutes (before walk)	NR	Final: Second walk, not specified	Baseline: 11 Followup: 11	Baseline: Mean 115.1 (SD 11.6) Followup: Mean 121.3 (SD 15.7)	Mean change from baseline: 6.2, (95% CI: -3.8 to 16.2), p=NS	NR SMD: -0.45 (95% CI: -1.34 to 0.45)	NR	
	Arm 2	FBT	Systolic blood pressure, at 0 minutes (before walk)	NR	Final: Second walk, not specified	Baseline: 9 Followup: 9	Baseline: Mean 121.9 (SD 12.7) Followup: Mean 121.9 (SD 14.5)	Mean change from baseline: 0, (95% CI: -7.1 to 7.1), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Systolic blood pressure, at 6 minutes (after walk)	NR	Final: Second walk, not specified	Baseline: 11 Followup: 11	Baseline: Mean 123.1 (SD 18.1) Followup: Mean 122.4 (SD 13.7)	Mean change from baseline: -0.7, (95% CI: -9.8 to 8.4), p=NS	NR SMD: -0.03 (95% CI: -0.91 to 0.85)	NR	
	Arm 2	FBT	Systolic blood pressure, at 6 minutes (after walk)	NR	Final: Second walk, not specified	Baseline: 9 Followup: 9	Baseline: Mean 131 (SD 13.1) Followup: Mean 129.9 (SD 10.4)	Mean change from baseline: -1.1, (95% CI: -11.2 to 9), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Systolic blood pressure, difference between 0-6 minutes	NR	Final: Second walk, not specified	Baseline: 11 Followup: 11	Baseline: Mean 8 (SD 15.7) Followup: Mean 1.1 (SD 16.5)	Mean change from baseline: -6.9, (95% CI: -20.8 to 7), p=NS	NR SMD: 0.42 (95% CI: -0.47 to 1.31)	NR	
	Arm 2	FBT	Systolic blood pressure, difference between 0-6 minutes	NR	Final: Second walk, not specified	Baseline: 9 Followup: 9	Baseline: Mean 9.1 (SD 10.5) Followup: Mean 8 (SD 10.4)	Mean change from baseline: -1.1, (95% CI: -13.6 to 11.3), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Diastolic blood pressure, at 0 minutes (before 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1.3, (95% CI: -0.6 to 3.2), p=NS	NR SMD: -1.10 (95% CI: -1.96 to -0.23)	NR	
	Arm 2	FPNS	Diastolic blood pressure, at 0 minutes (before 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -4.4, (95% CI: -8.1 to -0.7), p=Significant	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Diastolic blood pressure, at 0 minutes (before 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1.2, (95% CI: -1.9 to 4.2), p=NS	NR SMD: -0.37 (95% CI: -1.18 to 0.44)	NR	
	Arm 2	FPNS	Diastolic blood pressure, at 0 minutes (before 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -2.2, (95% CI: -8.9 to 4.5), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Diastolic blood pressure, at 6 minutes (after 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.3, (95% CI: -3.0 to 3.5), p=NS	NR SMD: 0.59 (95% CI: -0.23 to 1.40)	NR	
	Arm 2	FPNS	Diastolic blood pressure, at 6 minutes (after 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 4.7, (95% CI: -0.4 to 9.7), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Diastolic blood pressure, at 6 minutes (after 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.2, (95% CI: -3.7 to 4.0), p=NS	NR SMD: 0.22 (95% CI: -0.59 to 1.02)	NR	
	Arm 2	FPNS	Diastolic blood pressure, at 6 minutes (after 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1.6, (95% CI: -1.9 to 5.0), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Systolic blood pressure, at 0 minutes (before 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 3.1, (95% CI: -2.0 to 8.2), p=NS	NR SMD: -0.09 (95% CI: -0.89 to 0.71)	NR	
	Arm 2	FPNS	Systolic blood pressure, at 0 minutes (before 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1.5, (95% CI: -11.7 to 14.8), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Systolic blood pressure, at 0 minutes (before 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -0.7, (95% CI: -7.8 to 6.3), p=NS	NR SMD: 0.33 (95% CI: -0.48 to 1.13)	NR	
	Arm 2	FPNS	Systolic blood pressure, at 0 minutes (before 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 4.6, (95% CI: -6.3 to 15.5), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Systolic blood pressure, at 6 minutes (after 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -1.9, (95% CI: -9.2 to 5.3), p=NS	NR SMD: 0.95 (95% CI: 0.10 to 1.79)	NR	
	Arm 2	FPNS	Systolic blood pressure, at 6 minutes (after 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 10.4, (95% CI: 3.0 to 17.9), p=Significant	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Systolic blood pressure, at 6 minutes (after 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -3.1, (95% CI: -10.8 to 4.6), p=NS	NR SMD: 0.45 (95% CI: -0.36 to 1.26)	NR	
	Arm 2	FPNS	Systolic blood pressure, at 6 minutes (after 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 2.3, (95% CI: -3.6 to 8.1), p=NS	NA	NR	

6MWT=6 minute walk test; CI=confidence interval; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-45. Heart rate continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Gamborg, 2013 <sup>35</sup> Opioids vs Opioids	Arm 1	Red Morphine Drops	Pulse rate	NR	Final: 1 hour	Baseline: 9 Followup: 9	Baseline: Mean 98 (SD 14) Followup: Mean 93 (SD 14)	NR	Ref SMD: -0.07 (95% CI: -0.95 to 0.81)	NR	
	Arm 2	Subcutaneous Morphine	Pulse rate	NR	Final: 1 hour	Baseline: 11 Followup: 11	Baseline: Mean 93 (SD 14) Followup: Mean 87 (SD 16)	NR	Comparator: Arm 1 p=0.041	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Heart rate, beginning of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 90.5 (SD 16.6) Followup: Mean 87.7 (SD 13.5)	Mean change from baseline: - 2.9 (SD 10.2), p=0.38	NR SMD: 0.57 (95% CI: -0.11 to 1.26)	NR	
	Arm 2	Low dose fentanyl	Heart rate, beginning of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 77.6 (SD 13.9) Followup: Mean 79.5 (SD 15.4)	Mean change from baseline: 1.9 (SD 6.3), p=0.19	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Heart rate, end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 100.6 (SD 19.2) Followup: Mean 101.2 (SD 22.1)	Mean change from baseline: 0.5 (SD 16.5), p=NR	NR SMD: 0.02 (95% CI: -0.65 to 0.70)	NR	
	Arm 2	Low dose fentanyl	Heart rate, end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 87.5 (SD 26.8) Followup: Mean 88.3 (SD 29.6)	Mean change from baseline: 0.8 (SD 8.8), p=NR	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Heart rate, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 10.1 (SD 16) Followup: Mean 13.5 (SD 16.7)	Mean change from baseline: 3.4 (SD 12.5), p=0.15	NR SMD: -0.43 (95% CI: -1.11 to 0.25)	NR	
	Arm 2	Low dose fentanyl	Heart rate, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 9.9 (SD 23.25) Followup: Mean 8.8 (SD 22.9)	Mean change from baseline: - 1.1 (SD 8.3), p=0.64	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Charles, 2008 <sup>34</sup> Opioids vs Placebo	Arm 1	Nebulized saline	Pulse rate	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 107.1 (SD NR) Followup: Mean 94.4 (SD NR) Primary Followup: Mean 97.6 (SD NR)	Mean change from baseline: NR, (95% CI: - 1.72 to 20.62), p=NS	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures; For within arm comparison, only reported significance (95% CI and p-value)
	Arm 2	Nebulized hydromorphone	Pulse rate	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 101.6 (SD NR) Followup: Mean 90.8 (SD NR) Primary Followup: Mean 90.8 (SD NR)	Mean change from baseline: NR, (95% CI: 0.72 to 20.78), p<0.05	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures; For within arm comparison, only reported significance (95% CI and p-value)
	Arm 3	Systemic hydromorphone	Pulse rate	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 103.7 (SD NR) Followup: Mean 93 (SD NR) Primary Followup: Mean 98 (SD NR)	Mean change from baseline: NR, (95% CI: - 0.07 to 11.47), p=NS	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures; For within arm comparison, only reported significance (95% CI and p-value)
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Heart rate, at 0 minutes (before 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administrati on	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 0.3, (95% CI: - 6.3 to 5.6), p=NS	NR SMD: 0.12 (95% CI: -0.68 to 0.92)	NR	
	Arm 2	FPNS	Heart rate, at 0 minutes (before 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administrati on	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.8, (95% CI: - 3.3 to 4.9), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Heart rate, at 0 minutes (before 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administrati on	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.8, (95% CI: - 6.3 to 8.0), p=NS	NR SMD: -0.13 (95% CI: -0.93 to 0.67)	NR	
	Arm 2	FPNS	Heart rate, at 0 minutes (before 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administrati on	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 0.7, (95% CI: - 6.4 to 4.9), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Heart rate, at 6 minutes (after 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administrati on	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1.3, (95% CI: - 3.7 to 6.2), p=NS	NR SMD: 0 (95% CI: - 0.80 to 0.8001519)	NR	
	Arm 2	FPNS	Heart rate, at 6 minutes (after 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administrati on	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1.3, (95% CI: - 2.1 to 4.6), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Heart rate, at 6 minutes (after 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administrati on	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 1.4, (95% CI: - 6.4 to 3.7), p=NS	NR SMD: 0.25(95% CI: -0.55 to 1.05)	NR	
	Arm 2	FPNS	Heart rate, at 6 minutes (after 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administrati on	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.8, (95% CI: - 4.2 to 5.7), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Heart rate, at 0 minutes (before walk)	NR	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 82.9 (SD 16) Followup: Mean 83.9 (SD 16.3)	Mean change from baseline: 1, (95% CI: -4 to 6), p=NS	NR SMD: 0.07 (95% CI: -0.81 to 0.95)	NR	
	Arm 2	FBT	Heart rate, at 0 minutes (before walk)	NR	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 90.6 (SD 12.9) Followup: Mean 92.6 (SD 12.8)	Mean change from baseline: 2, (95% CI: -3.8 to 7.8), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Heart rate, at 6 minutes (after walk)	NR	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 83.5 (SD 19.6) Followup: Mean 88.5 (SD 2.1)	Mean change from baseline: 5, (95% CI: -10 to 20), p=NS	NR SMD: -0.51 (95% CI: -1.40 to 0.39)	NR	
	Arm 2	FBT	Heart rate, at 6 minutes (after walk)	NR	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 97.9 (SD 13.7) Followup: Mean 94.6 (SD 11.9)	Mean change from baseline: - 3.3, (95% CI: - 8.4 to 1.7), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Heart rate, difference between 0-6 minutes	NR	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 0.6 (SD 16.2) Followup: Mean 4.6 (SD 11.6)	Mean change from baseline: 4, (95% CI: -14.1 to 22.1), p=NS	NR SMD: -0.77 (95% CI: -1.69 to 0.143)	NR	
	Arm 2	FBT	Heart rate, difference between 0-6 minutes	NR	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 7.3 (SD 9.2) Followup: Mean 2 (SD 5.1)	Mean change from baseline: - 5.3, (95% CI: - 13.4 to 2.7), p=NS	NA	NR	

CI=confidence interval; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-46. Functional status (6 minute walk) continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Walk distance at 6 minutes	6MWT	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 399 (SD 86.4) Followup: Mean 417.9 (SD 89.3)	Mean change from baseline: 18.9, (95% CI: -10.4 to 48.2), p=NS	NR SMD: 0.20(95% CI: -0.68 to 1.08)	NR	
	Arm 2	Fentanyl	Walk distance at 6 minutes	6MWT	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 397.7 (SD 98.1) Followup: Mean 434.9 (SD 95.4)	Mean change from baseline: 37.2, (95% CI: 5.8 to 68.6), p=Significant	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Walk distance at 6 minutes, at 0 minutes (after 6 MWT)	6MWT	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 371.2 (SD 114.2) Followup: Mean 387.5 (SD 111.3)	Mean change from baseline: 16.3, (95% CI: -8.6 to 41.3), p=NS	NR SMD: 0.08(95% CI: -0.72 to 0.88)	NR	
	Arm 2	FPNS	Walk distance at 6 minutes, at 0 minutes (after 6 MWT)	6MWT	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 321.8 (SD 80.6) Followup: Mean 345.5 (SD 79.7)	Mean change from baseline: 23.8, (95% CI: 1.3 to 46.2), p=Significant	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Walk distance at 6 minutes, at 0 minutes (after 6 MWT)	6MWT	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 371.2 (SD 114.2) Followup: Mean 391.3 (SD 112.1)	Mean change from baseline: 14.6, (95% CI: -11.0 to 40.3), p=NS	NR SMD: 0.09 (95% CI: -0.712 to 0.89)	NR	
	Arm 2	FPNS	Walk distance at 6 minutes, at 0 minutes (after 6 MWT)	6MWT	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 321.8 (SD 80.6) Followup: Mean 345 (SD 80.5)	Mean change from baseline: 23.3, (95% CI: -1.7 to 48.2), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Walk distance at 6 minutes	6MWT	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 373.1 (SD 92.5) Followup: Mean 379.8 (SD 92.4)	Mean change from baseline: 6.7, (95% CI: -3.4, 16.9), p=NS	NR SMD: -0.09 (95% CI: -0.97 to 0.79)	NR	
	Arm 2	FBT	Walk distance at 6 minutes	6MWT	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 410.9 (SD 80.3) Followup: Mean 409.9 (SD 81.8)	Mean change from baseline: -1, (95% CI: -22.3, 20.3), p=NS	NA	NR	
Pinna, 2015 <sup>46</sup> Opioids vs Placebo	Arm 1	Placebo	Distance covered in 6 minute walk test, First visit	6MWT	Final: After 6 minute walk	Baseline: 6 Followup: 6	Baseline: NR Followup: Medium 563.3 (SD 45), Range: 480 to 610	NR	NR	Possible period effect	
	Arm 2	Fentanyl citrate	Distance covered in 6 minute walk test, First visit	6MWT	Final: After 6 minute walk	Baseline: 7 Followup: 7	Baseline: NR Followup: Medium 591.4 (SD 117.5), Range: 410 to 720	NR	NR	Possible period effect	
Pinna, 2015 <sup>46</sup> Opioids vs Placebo	Arm 1	Placebo	Distance covered in 6 minute walk test, First visit	6MWT	Final: After 6 minute walk	Baseline: 6 Followup: 6	Baseline: NR Followup: Median 570 (SD NR), Range: Q1/Q3: 560/590	NR	NR	Possible period effect	
	Arm 2	Fentanyl citrate	Distance covered in 6 minute walk test, First visit	6MWT	Final: After 6 minute walk	Baseline: 7 Followup: 7	Baseline: NR Followup: Median 620 (SD NR), Range: Q1/Q3: 480/690	NR	NR	Possible period effect	
Pinna, 2015 <sup>46</sup> Opioids vs Placebo	Arm 1	Placebo	Distance covered in 6 minute walk test, Second visit	6MWT	Final: After 6 minute walk	Baseline: 6 Followup: 6	Baseline: NR Followup: Medium 528.3 (SD 101.3), Range: 340 to 640	NR	NR	Possible period effect	
	Arm 2	Fentanyl citrate	Distance covered in 6 minute walk test, Second visit	6MWT	Final: After 6 minute walk	Baseline: 7 Followup: 7	Baseline: NR Followup: Medium 660.7 (SD 188.8), Range: 530 to 1065	NR	NR	Possible period effect	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Pinna, 2015 <sup>46</sup> Opioids vs Placebo	Arm 1	Placebo	Distance covered in 6 minute walk test, Second visit	6MWT	Final: After 6 minute walk	Baseline: 6 Followup: 6	Baseline: NR Followup: Median 545 (SD NR), Range: Q1/Q3: 520/580	NR	NR	Possible period effect	
	Arm 2	Fentanyl citrate	Distance covered in 6 minute walk test, Second visit	6MWT	Final: After 6 minute walk	Baseline: 7 Followup: 7	Baseline: NR Followup: Median 560 (SD NR), Range: Q1/Q3: 560/710	NR	NR	Possible period effect	

6MWT=6 minute walk test; CI=confidence interval; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-47. Oxygen saturation continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Oxygen saturation	NR	Final: 90 minutes	Baseline: 31 Followup: 31	Baseline: Mean 0.944 (SD 2.2) Followup: Mean 0.941 (SD 1.3)	NR	NR SMD: 0.001 (95% CI: -0.49 to 0.50)	NR	
	Arm 2	Midazolam	Oxygen saturation	NR	Final: 90 minutes	Baseline: 32 Followup: 32	Baseline: Mean 0.948 (SD 1.2) Followup: Mean 0.947 (SD 1)	NR	NA	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Oxygen saturation	NR	Final: 5 days	Baseline: 31 Followup: 30	Baseline: Mean 0.944 (SD 2.2) Followup: Mean 0.946 (SD 1)	NR	NR SMD: -0.002 (95% CI: -0.50 to 0.49)	NR	
	Arm 2	Midazolam	Oxygen saturation	NR	Final: 5 days	Baseline: 32 Followup: 31	Baseline: Mean 0.948 (SD 1.2) Followup: Mean 0.946 (SD 1.1)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Oxygen saturation	NR	Final: 48 hours	Baseline: 35 Followup: 24	Baseline: Mean 0.72 (SD NR), Range: 95% CI: 68 to 74 Followup: Mean 0.7 (SD NR), Range: 95% CI: 66 to 74	p=NS	Comparator: Between all arms p=NS	NR	No significant differences for inter- or intragroup comparisons
	Arm 2	Midazolam	Oxygen saturation	NR	Final: 48 hours	Baseline: 33 Followup: 23	Baseline: Mean 0.73 (SD NR), Range: 95% CI: 67 to 74 Followup: Mean 0.7 (SD NR), Range: 95% CI: 67 to 71.5	p=NS	Comparator: Between all arms p=NS	NR	No significant differences for inter- or intragroup comparisons
	Arm 3	Morphine+ Midazolam	Oxygen saturation	NR	Final: 48 hours	Baseline: 33 Followup: 23	Baseline: Mean 0.73 (SD NR), Range: 95% CI: 68 to 75 Followup: Mean 0.715 (SD NR), Range: 95% CI: 67 to 73	p=NS	Comparator: Between all arms p=NS	NR	No significant differences for inter- or intragroup comparisons



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Oxygen saturation, beginning of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 97.7 (SD 1.4) Followup: Mean 96.7 (SD 2.1)	Mean change from baseline: -1 (SD 1.2), p=0.02	NR SMD: 0.80 (95% CI: 0.10 to 1.51)	NR	
	Arm 2	Low dose fentanyl	Oxygen saturation, beginning of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 97.2 (SD 2) Followup: Mean 97.2 (SD 2.2)	Mean change from baseline: 0.1 (SD 1.5), p=0.95	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Oxygen saturation, end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 97.9 (SD 2) Followup: Mean 97.6 (SD 1.9)	Mean change from baseline: -0.3 (SD 1), p=NR	NR SMD: 0.24 (95% CI: -0.43 to 0.92)	NR	
	Arm 2	Low dose fentanyl	Oxygen saturation, end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 97.9 (SD 2.2) Followup: Mean 97.9 (SD 2.8)	Mean change from baseline: 0 (SD 1.4), p=NR	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Oxygen saturation, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 0.2 (SD 1.2) Followup: Mean 0.9 (SD 1)	Mean change from baseline: 0.7 (SD 1.7), p=0.21	NR SMD: -0.47 (95% CI: -1.15 to 0.213)	NR	
	Arm 2	Low dose fentanyl	Oxygen saturation, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 0.7 (SD 2) Followup: Mean 0.7 (SD 1.5)	Mean change from baseline: -0.1 (SD 1.7), p=0.87	NA	NR	
Simon, 2016 <sup>47</sup> Opioids vs Opioids	Arm 1	Immediate release morphine	Oxygen saturation	NR	Final: 60 minutes	Baseline: 10 Final: 6	Baseline: Mean 89.5 (SD 6.9) Final: Mean 91.8 (SD 4.7)	NR	NR	NR	
	Arm 2	Fentanyl buccal tablet	Oxygen saturation	NR	Final: 60 minutes	Baseline: 10 Final: 6	Baseline: Mean 90.9 (SD 5.3) Final: Mean 92 (SD 3)	NR	NR SMD: -0.22 (95% CI: -1.10 to 0.66)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 1993 <sup>32</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, %	NR	Final: 60 minutes	Baseline: 10 Final: 10	Baseline: Mean 92 (SD 1) Final: Mean 92 (SD 2)	NR	Ref	NR	
	Arm 2	Morphine	Oxygen saturation, %	NR	Final: 60 minutes	Baseline: 10 Final: 10	Baseline: Mean 92 (SD 2) Final: Mean 92 (SD 2)	NR	Comparator: Arm1 Difference in mean: NR Baseline difference between arms: p>0.2; Followup difference between arms: p>0.2 SMD: 0.0 (95% CI: - 0.88 to 0.88)	NR	
Charles, 2008 <sup>34</sup> Opioids vs Placebo	Arm 1	Nebulized saline	Oxygen saturation	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 89.7 (SD NR) Followup: Mean 91.8 (SD NR) Primary Followup: Mean 91.8 (SD NR)	Mean change from baseline: NR, (95% CI: -4.10 tp - 0.10), p<0.05	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures; For within arm comparison, only reported significance (95% CI and p-value)
	Arm 2	Nebulized hydromorp hone	Oxygen saturation	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 89.8 (SD NR) Followup: Mean 92.3 (SD NR) Primary Followup: Mean 91.7 (SD NR)	Mean change from baseline: NR, (95% CI: -5.48 to 1.68), p=NS	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures; For within arm comparison, only reported significance (95% CI and p-value)
	Arm 3	Systemic hydromorp hone	Oxygen saturation	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 91.4 (SD NR) Followup: Mean 92.8 (SD NR) Primary Followup: Mean 91.9 (SD NR)	Mean change from baseline: NR, (95% CI: -4.01 to 3.01), p=NS	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures; For within arm comparison, only reported significance (95% CI and p-value)



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, 0 minutes	NR	Final: Second walk, not specified	Baseline: 10 Followup: 10	Baseline: Mean 95 (SD 2.2) Followup: Mean 96.2 (SD 1.9)	Mean change from baseline: 1.2, (95% CI: -0.6 to 3), p=NS	NR SMD: -0.80 (95% CI: -1.71 to 0.12)	NR	
	Arm 2	Fentanyl	Oxygen saturation, 0 minutes	NR	Final: Second walk, not specified	Baseline: 10 Followup: 10	Baseline: Mean 97.1 (SD 2.2) Followup: Mean 96.5 (SD 2.6)	Mean change from baseline: -0.6, (95% CI: -1.6 to 0.4), p=NS	NA	NR	
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, 6 minutes	NR	Final: Second walk, not specified	Baseline: 10 Followup: 10	Baseline: Mean 95.3 (SD 3.1) Followup: Mean 96.1 (SD 1.9)	Mean change from baseline: 0.8, (95% CI: -1.6 to 3.2), p=NS	NR SMD: -0.79 (95% CI: -1.70 to 0.12)	NR	
	Arm 2	Fentanyl	Oxygen saturation, 6 minutes	NR	Final: Second walk, not specified	Baseline: 10 Followup: 10	Baseline: Mean 98 (SD 2.3) Followup: Mean 96.8 (SD 2.4)	Mean change from baseline: -1.2, (95% CI: -2.7 to 0.3), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, at 0 minutes	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.1, (95% CI: -1 to 1.1), p=NS	NR SMD: -0.32 (95% CI: -1.12 to 0.49)	NR	
	Arm 2	FPNS	Oxygen saturation, at 0 minutes	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -0.5, (95% CI: -1.6 to 0.6), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, at 0 minutes	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1, (95% CI: - 0.4 to 2.4), p=NS	NR SMD: -0.37 (95% CI: -1.18 to 0.44)	NR	
	Arm 2	FPNS	Oxygen saturation, at 0 minutes	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.2, (95% CI: -0.8 to 1.2), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, at 6 minutes	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -0.2, (95% CI: -1.3 to 1), p=NS	NR SMD: 0.30 (95% CI: -0.50 to 1.11)	NR	
	Arm 2	FPNS	Oxygen saturation, at 6 minutes	NR	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.4, (95% CI: -0.7 to 1.5), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, at 6 minutes	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -1.1, (95% CI: -2.3 to 0.1), p=NS	NR SMD: 0.46 (95% CI: -0.35 to 1.27)	NR	
	Arm 2	FPNS	Oxygen saturation, at 6 minutes	NR	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -0.2, (95% CI: -1.2 to 0.8), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, at 0 minutes (before walk)	Oxygen saturation	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 97.1 (SD 2.2) Followup: Mean 97.3 (SD 1.2)	Mean change from baseline: 0.2, (95% CI: -1.2 to 1.5), p=NS	NR SMD: 0.06 (95% CI: -0.82 to 0.94)	NR	
	Arm 2	FBT	Oxygen saturation, at 0 minutes (before walk)	Oxygen saturation	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 97.9 (SD 1.5) Followup: Mean 98.2 (SD 0.8)	Mean change from baseline: 0.3, (95% CI: -0.5 to 1.2), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, at 6 minutes (after walk)	Oxygen saturation	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 97.4 (SD 1.8) Followup: Mean 96.8 (SD 2.5)	Mean change from baseline: -0.5, (95% CI: -1.9 to 0.9), p=NS	NR SMD: 0.05 (95% CI: -0.83 to 0.93)	NR	
	Arm 2	FBT	Oxygen saturation, at 6 minutes (after walk)	Oxygen saturation	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 98.3 (SD 1.9) Followup: Mean 97.9 (SD 1.9)	Mean change from baseline: -0.4, (95% CI: -1.5 to 0.6), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation, difference between 0-6 minutes	Oxygen saturation	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 0.1 (SD 2.8) Followup: Mean -0.5 (SD 2.2)	Mean change from baseline: -0.6, (95% CI: -3 to 1.8), p=NS	NR SMD: -0.09 (95% CI: -0.97 to 0.79)	NR	
	Arm 2	FBT	Oxygen saturation, difference between 0-6 minutes	Oxygen saturation	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 0.4 (SD 1.7) Followup: Mean -0.3 (SD 1.4)	Mean change from baseline: -0.8, (95% CI: -2.2 to 0.6), p=NS	NA	NR	
Pinna, 2015 <sup>46</sup> Opioids vs Placebo	Arm 1	Placebo	Oxygen saturation	NR	Final: After 6 minute walk	Baseline: 13 Followup: 13	Baseline: Mean 93.8 (SD 3.8), Range: 89 to 99 Followup: Mean 91.5 (SD 5.8), Range: 78 to 98	NR	NR SMD: -0.12 (95% CI: -0.89 to 0.65)	NR	We calculated these outcomes given individual patient data
	Arm 2	Fentanyl citrate	Oxygen saturation	NR	Final: After 6 minute walk	Baseline: 13 Followup: 13	Baseline: Mean 93.2 (SD 3.6), Range: 83 to 97 Followup: Mean 90.3 (SD 5.4), Range: 77 to 98	NR	NA	NR	We calculated these outcomes given individual patient data

CI=confidence interval; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-48. Respiratory rate continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Allard, 1999 <sup>3</sup> Opioids vs Opioids <sup>1</sup>	Arm 1	Opioid dose 25% of 4 hourly regular dose	Respiratory frequency	NR	Final: 240 minutes	Baseline: 18 Followup: 18	Baseline: Mean 20.1 (SD NR) Followup: Mean 19.1 (SD NR)	NR	NR	NR	Followup data from figure, not text
	Arm 2	Opioid dose 50% of 4 hourly regular dose	Respiratory frequency	NR	Final: 240 minutes	Baseline: 15 Followup: 15	Baseline: Mean 20.6 (SD NR) Followup: Mean 18.5 (SD NR)	NR	NR	NR	Followup data from figure, not text
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Respiratory rate, beginning of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 17.4 (SD 3.5) Followup: Mean 16 (SD 3.7)	Mean change from baseline: -1.4 (SD 3.3), p=0.17	NR SMD: 0.45 (95% CI: -0.23 to 1.13)	NR	
	Arm 2	Low dose fentanyl	Respiratory rate, beginning of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 15.5 (SD 3.4) Followup: Mean 15.4 (SD 4)	Mean change from baseline: -0.1 (SD 2.5), p=0.95	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Respiratory rate, end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 21.1 (SD 3) Followup: Mean 20.9 (SD 4.9)	Mean change from baseline: -0.2 (SD 4.1), p=NR	NR SMD: -0.35 (95% CI: -1.02 to 0.33)	NR	
	Arm 2	Low dose fentanyl	Respiratory rate, end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 20.4 (SD 6.2) Followup: Mean 18.8 (SD 5.2)	Mean change from baseline: -1.6 (SD 4), p=NR	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Respiratory rate, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 3.7 (SD 4.1) Followup: Mean 4.9 (SD 5.3)	Mean change from baseline: 1.2 (SD 6.4), p=0.72	NR SMD: -0.52 (95% CI: -1.21 to 0.16)	NR	
	Arm 2	Low dose fentanyl	Respiratory rate, Difference between beginning and end of walk	NR	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 4.9 (SD 4.4) Followup: Mean 3.5 (SD 4.1)	Mean change from baseline: -1.5 (SD 3.8), p=0.15	NA	NR	
Simon, 2016 <sup>47</sup> Opioids vs Opioids	Arm 1	Immediate release morphine	Respiratory rate	NR	Final: 60 minutes	Baseline: 10 Final: 6	Baseline: Mean 15.7 (SD 3.8) Final: Mean 16 (SD 2.8)	NR	NR	NR	
	Arm 2	Fentanyl buccal tablet	Respiratory rate	NR	Final: 60 minutes	Baseline: 10 Final: 6	Baseline: Mean 15.7 (SD 3.8) Final: Mean 15.4 (SD 5)	NR	NR SMD: -0.6 (95% CI: -6.52 to 5.32)	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 1993 <sup>32</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, breaths/min	NR	Final: 60 minutes	Baseline: 10 Final: 10	Baseline: Mean 23 (SD 9) Final: Mean 22 (SD 10)	NR	Ref	NR	
	Arm 2	Morphine	Respiratory rate, breaths/min	NR	Final: 60 minutes	Baseline: 10 Final: 10	Baseline: Mean 22 (SD 9) Final: Mean 24 (SD 8)	NR	Comparator: Arm1 Difference in mean: NR Baseline difference between arms: p>0.2; Followup difference between arms: p>0.2 SMD: 3.0 (95% CI: -10.69 to 16.69)	NR	
Charles, 2008 <sup>34</sup> Opioids vs Placebo	Arm 1	Nebulized saline	Respiratory rate	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 26.1 (SD NR) Followup: Mean 21.3 (SD NR) Primary Followup: Mean 21.9 (SD NR)	Mean change from baseline: NR, (95% CI: 2.08 to 6.32), p<0.05	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures;
	Arm 2	Nebulized hydromorphone	Respiratory rate	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 25.9 (SD NR) Followup: Mean 20.8 (SD NR) Primary Followup: Mean 22.2 (SD NR)	Mean change from baseline: NR, (95% CI: 1.34 to 6.06), p<0.05	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures;
	Arm 3	Systemic hydromorphone	Respiratory rate	NR	Final: 1 hour Primary: 10 minutes	Baseline: 20 Followup: 20 Primary FU: 20	Baseline: Mean 26.4 (SD NR) Followup: Mean 19.5 (SD NR) Primary Followup: Mean 21.7 (SD NR)	Mean change from baseline: NR, (95% CI: 1.86 to 7.54), p<0.05	Comparator: Between all arms p=NS	NR	Follow-up data at 1 hour taken from figures;



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, 0 minutes	NR	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 18.6 (SD 1.3) Followup: Mean 18.6 (SD 1.3)	Mean change from baseline: 0, (95% CI: -1 to 1), p=NS	NR SMD: -0.27 (95% CI: -1.15 to 0.61)	NR	
	Arm 2	Fentanyl	Respiratory rate, 0 minutes	NR	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 18.8 (SD 3.3) Followup: Mean 18.2 (SD 1.8)	Mean change from baseline: -0.6, (95% CI: - 3.5 to 2.3), p=NS	NA	NR	
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, 6 minutes	NR	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 24.6 (SD 5.7) Followup: Mean 23.4 (SD 3.9)	Mean change from baseline: -1.2, (95% CI: - 4.6 to 2.2), p=NS	NR SMD: -0.29 (95% CI: -1.18to 0.59)	NR	
	Arm 2	Fentanyl	Respiratory rate, 6 minutes	NR	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 23.4 (SD 2.7) Followup: Mean 21 (SD 2.9)	Mean change from baseline: -2.4, (95% CI: - 4.5 to -0.3), p=Significant	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, at 0 minutes (before 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administra tion	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -0.2, (95% CI: - 1.5 to 1.2), p=NS	NR	NR	
	Arm 2	FPNS	Respiratory rate, at 0 minutes (before 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administra tion	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.9, (95% CI: - 0.2 to 2.0), p=NS	NR	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, at 0 minutes (before 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administra tion	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -0.5, (95% CI: - 1.7 to 0.6), p=Significant	NR	NR	
	Arm 2	FPNS	Respiratory rate, at 0 minutes (before 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administra tion	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1.2, (95% CI: 0.1 to 2.3), p=Significant	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, at 6 minutes (after 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administra tion	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -1.3, (95% CI: - 2.4 to -0.2), p=Significant	NR SMD: 0.67 (95% CI: -0.15 to 1.50)	NR	
	Arm 2	FPNS	Respiratory rate, at 6 minutes (after 6 MWT)	NR	Final: Second Walk, 20 minutes after first drug administra tion	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.3, (95% CI: - 1.3 to 1.8), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, at 6 minutes (after 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administra tion	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: -1.6, (95% CI: - 2.6 to -0.6), p=Significant	NR SMD: 0.90 (95% CI: 0.06 to 1.75)	NR	
	Arm 2	FPNS	Respiratory rate, at 6 minutes (after 6 MWT)	NR	Final: Third Walk, same day, 20 minutes after second drug administra tion	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.3, (95% CI: - 1.1 to 1.6), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, at 0 minutes (before walk)	NR	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 17.5 (SD 4.6) Followup: Mean 17.5 (SD 3.4)	Mean change from baseline: 0.1, (95% CI: - 2.4 to 2.5), p=NS	NR SMD: 0.03 (95% CI: -0.85 to 0.91)	NR	
	Arm 2	FBT	Respiratory rate, at 0 minutes (before walk)	NR	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 17.7 (SD 3.1) Followup: Mean 17.9 (SD 2.9)	Mean change from baseline: 0.2, (95% CI: - 1.2 to 1.6), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, at 6 minutes (after walk)	NR	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 20.3 (SD 5.2) Followup: Mean 19.3 (SD 4)	Mean change from baseline: -1, (95% CI: - 3.5 to 1.5), p=NS	NR SMD: -0.32 (95% CI: -1.21 to 0.56)	NR	
	Arm 2	FBT	Respiratory rate, at 6 minutes (after walk)	NR	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 20.4 (SD 2.9) Followup: Mean 18.1 (SD 2.9)	Mean change from baseline: -2.3, (95% CI: - 3.9 to -0.8), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Respiratory rate, difference between 0-6 minutes	NR	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 2.8 (SD 3.4) Followup: Mean 1.7 (SD 3.4)	Mean change from baseline: -1.1, (95% CI: - 3.5 to 1.3), p=NS	NR SMD: -0.49 (95% CI: -1.39 to 0.407)	NR	
	Arm 2	FBT	Respiratory rate, difference between 0-6 minutes	NR	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 2.8 (SD 2.9) Followup: Mean 0.2 (SD 1.2)	Mean change from baseline: -2.6, (95% CI: - 4.7 to -0.4), p=Significant	NA	NR	

6MWT=6 minute walk test; CI=confidence interval; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-49. No adverse events reported for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Outcome Definition	Tool	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Gamborg, 2013 <sup>35</sup> Opioids vs Opioids	Overall	NR	NR	Final: NR	Baseline: NR Followup: NR	Baseline: NR Followup: NR	NR	NR	NR	

N=sample size; NR=not reported



**Evidence Table D-50. Central nervous (dizziness) continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dizziness	NRS	Final: After second walk, ~20 minutes	Baseline: 16 Followup: 13	Baseline: NR Followup: NR	Mean change from baseline: -0.2 (SD 0.7), p=NR	NR SMD: -0.54 (95% CI: -1.23 to 0.14)	NR	
	Arm 2	Low dose fentanyl	Dizziness	NRS	Final: After second walk, ~20 minutes	Baseline: 18 Followup: 17	Baseline: NR Followup: NR	Mean change from baseline: 0.24 (SD 0.9), p=NR	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Dizzy	NRS	NR	Baseline: NR Followup: NR	Baseline: NR Followup: NR	Mean change from baseline: 0.2 (SD 0.4), p=NR	NR	NR	
	Arm 2	FBT	Dizzy	NRS	NR	Baseline: NR Followup: NR	Baseline: NR Followup: NR	Mean change from baseline: -0.4 (SD 1.3), p=NR	NR	NR	

CI=confidence interval; FBT= fentanyl buccal tablet; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-51. Central nervous (dizziness) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Anxiolytics vs Combination	Arm 2	Midazolam	Dizziness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Morphine+Midazolam	Dizziness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Tian, 2016 <sup>48</sup> Corticosteroids vs Bronchodilators	Arm 2	Methylprednisolone	Dizziness	NR	Final: 1 hour	Followup: 111	0/111 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Aminophylline	Dizziness	NR	Final: 1 hour	Followup: 114	0/114 (0)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Dizziness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	1/35 (2.9)	NR	NR RR: 0.35 (95% CI: 0.01 to 8.37)	NR	
	Arm 2	Midazolam	Dizziness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Tian, 2016 <sup>48</sup> Opioids vs Bronchodilators	Arm 1	Morphine	Dizziness	NR	Final: 1 hour	Followup: 118	19/118 (16.1)	NR	NR RR: 0.03 (95% CI: 0 to 0.43)	NR	
	Arm 3	Aminophylline	Dizziness	NR	Final: 1 hour	Followup: 114	0/114 (0)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Tian, 2016 <sup>48</sup> Opioids vs Corticosteroids	Arm 1	Morphine	Dizziness	NR	Final: 1 hour	Followup: 118	19/118 (16.1)	NR	NR RR: 0.03 (95% CI: 0 to 0.45)	NR	
	Arm 2	Methylprednisolone	Dizziness	NR	Final: 1 hour	Followup: 111	0/111 (0)	NR	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Dizziness	NRS	Final: After second walk, ~20 min after	Followup: 13	1/13 (7.7)	NR	NR RR: 0.26 (95% CI: 0.03 to 1.98)	NR	
	Arm 2	Low dose fentanyl	Dizziness	NRS	Final: After second walk, ~20 min after	Followup: 17	5/17 (29.4)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Combination	Arm 1	Morphine	Dizziness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	1/35 (2.9)	NR	NR RR: 0.35 (95% CI: 0.01 to 8.37)	NR	
	Arm 3	Morphine+Midazolam	Dizziness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dizziness (after second walk)	11 point NRS	Final: 30 minutes	Followup: 12	2/12 (18.2)	NR	Ref RR: 1 (95% CI: 0.17 to 5.98)	NR	
	Arm 2	FPNS	Dizziness (after second walk)	11 point NRS	Final: 30 minutes	Followup: 12	2/12 (18.2)	NR	Comparator: Arm 1 Difference in N: p=NR	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Dizziness (after third walk)	11 point NRS	Final: 30 minutes	Followup: 12	1/12 (10)	NR	Ref RR: 5 (95% CI: 0.68 to 36.66)	NR	
	Arm 2	FPNS	Dizziness (after third walk)	11 point NRS	Final: 30 minutes	Followup: 12	5/12 (45.5)	NR	Comparator: Arm 1 Difference in N: p=0.07	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Dizzy, with worse scores after 6MWT	NRS	Final: After medication administration (not specified)	Followup: 11	2/11 (18.2)	NR	NR RR: 0.24 (95% CI: 0.01 to 4.44)	NR	
	Arm 2	FBT	Dizzy, with worse scores after 6MWT	NRS	Final: After medication administration (not specified)	Followup: 9	0/9 (0)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hardy, 2016 <sup>36</sup> Anxiolytics vs Placebo	Overall	Overall	Dizziness worst than baseline, Grade 1	NCI Common Terminolog y Criteria for Adverse Events	Final: 14 days	Followup: 62	3/62 (4.8)	NR	NR	NR	
Hardy, 2016 <sup>36</sup> Anxiolytics vs Placebo	Overall	Overall	Dizziness worst than baseline, Grade 2	NCI Common Terminolog y Criteria for Adverse Events	Final: 14 days	Followup: 62	0/62 (0)	NR	NR	NR	
Hardy, 2016 <sup>36</sup> Anxiolytics vs Placebo	Overall	Overall	Dizziness worst than baseline, Grade 3	NCI Common Terminolog y Criteria for Adverse Events	Final: 14 days	Followup: 62	0/62 (0)	NR	NR	NR	

CI=confidence interval; CTC=; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation; SE=standard error



**Evidence Table D-52. Central nervous (drowsiness) continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Drowsiness	NRS	Final: After second walk, ~20 minutes	Baseline: 16 Followup: 13	Baseline: NR Followup: NR	Mean change from baseline: 0 (SD 2.4), p=NR	NR SMD: 0.17 (95% CI: -0.50 to 0.85)	NR	
	Arm 2	Low dose fentanyl	Drowsiness	NRS	Final: After second walk, ~20 minutes	Baseline: 18 Followup: 17	Baseline: NR Followup: NR	Mean change from baseline: -0.3 (SD 0.7), p=NR	NA	NR	
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Drowsiness	ESAS Drowsiness	Final: 7 days	Baseline: 19 Followup: 14	Baseline: Mean 1.8 (SD 2.2) Followup: Mean 2.4 (SD 1.9)	Mean change from baseline: 1.1 (SD 2.1), p=NR	Ref SMD: -1.10 (95% CI: -1.78 to -0.41)	NR	
	Arm 2	Dexamethasone	Drowsiness	ESAS Drowsiness	Final: 7 days	Baseline: 19 Followup: 16	Baseline: Mean 3.7 (SD 2.7) Followup: Mean 2.3 (SD 2.3)	Mean change from baseline: -1.8 (SD 3.1), p=NR	Comparator: Arm 1 p=0.01	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Drowsy	NRS	NR	Baseline: NR Followup: NR	Baseline: NR Followup: NR	Mean change from baseline: 0.6 (SD 2.3), p=NR	NR	NR	
	Arm 2	FBT	Drowsy	NRS	NR	Baseline: NR Followup: NR	Baseline: NR Followup: NR	Mean change from baseline: -0.1 (SD 0.3), p=NR	NR	NR	
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Drowsiness	Numeric Rating Scale, 11-point	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: NR Followup: Mean 0 (SD NR), IQR: -3.25 to 0	NR	Ref	NR	
	Arm 2	Fentanyl	Drowsiness	Numeric Rating Scale, 11-point	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: NR Followup: Mean 0 (SD NR), IQR: -0.75 to 0	NR	Comparator: Arm 1 p=0.48	NR	

CI=confidence interval; CTC=; ESAS= Edmonton Symptom Assessment Scale; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-53. Central nervous (drowsiness) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Drowsiness	NRS	Final: After second walk, ~20 min after	Followup: 13	2/13 (15.4)	NR	NR RR: 2.62 (95% CI: 0.27 to 25.81)	NR	
	Arm 2	Low dose fentanyl	Drowsiness	NRS	Final: After second walk, ~20 min after	Followup: 17	1/17 (5.9)	NR	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Drowsiness (after second walk)	11 point NRS	Final: 30 minutes	Followup: 12	2/12 (16.7)	NR	Ref RR: 0.5 (95% CI: 0.05 to 4.81)	NR	
	Arm 2	FPNS	Drowsiness (after second walk)	11 point NRS	Final: 30 minutes	Followup: 12	1/12 (8.3)	NR	Comparator: Arm 1 Difference in N: p=NR	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Drowsiness (after third walk)	11 point NRS	Final: 30 minutes	Followup: 12	5/12 (45.5)	NR	Ref RR: 0.20 (95% CI: 0.03 to 1.47)	NR	
	Arm 2	FPNS	Drowsiness (after third walk)	11 point NRS	Final: 30 minutes	Followup: 12	1/12 (1)	NR	Comparator: Arm 1 Difference in N: p=0.04	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Drowsy, with worse scores after 6MWT	NRS	Final: After medication administration (not specified)	Followup: 11	2/11 (18.2)	NR	NR RR: 0.24 (95% CI: 0.01 to 4.44)	NR	
	Arm 2	FBT	Drowsy, with worse scores after 6MWT	NRS	Final: After medication administration (not specified)	Followup: 9	0/9 (0)	NR	NA	NR	

6MWT=6 minute walk test; CI=confidence interval; CTC=; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-54. Central nervous (fatigue) continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Fatigue, beginning of walk	Borg scale	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 2.8 (SD 2.4) Followup: Mean 2.3 (SD 1.7)	Mean change from baseline: - 0.5 (SD 1.5), p=0.31	NR SMD: 0 (95% CI: - 0.67 to 0.67)	NR	
	Arm 2	Low dose fentanyl	Fatigue, beginning of walk	Borg scale	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 2.4 (SD 2.6) Followup: Mean 1.9 (SD 2.3)	Mean change from baseline: - 0.5 (SD 1.1), p=0.1	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Fatigue, Difference between beginning and end of walk	Borg scale	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 2 (SD 3) Followup: Mean 1 (SD 1)	Mean change from baseline: - 1 (SD 2.8), p=0.13	NR SMD: -0.53 (95% CI: -1.22 to 0.15)	NR	
	Arm 2	Low dose fentanyl	Fatigue, Difference between beginning and end of walk	Borg scale	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 1.4 (SD 2.5) Followup: Mean 1.5 (SD 2.3)	Mean change from baseline: 0.2 (SD 1.6), p=0.64	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Fatigue, end of walk	Borg scale	Final: Second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 4.8 (SD 1.9) Followup: Mean 3.3 (SD 1.9)	Mean change from baseline: - 1.5 (SD 2.7), p=NR	NR SMD: -0.54 (95% CI: -1.22 to 0.15)	NR	
	Arm 2	Low dose fentanyl	Fatigue, end of walk	Borg scale	Final: Second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 4.1 (SD 1.8) Followup: Mean 3.5 (SD 1.9)	Mean change from baseline: - 0.4 (SD 1.2), p=NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Fatigue	ESAS Fatigue	Final: 14 Days Primary: 7 days	Baseline: 19 Followup: 15 Primary FU: 14	Baseline: Mean 3.4 (SD 2.8) Followup: Mean 3.3 (SD 1.9) Primary Followup: Mean 3.4 (SD 2.2)	Mean change from baseline: 0.5 (SD 2.8), p=NR	Ref SMD: -0.54 (95% CI: -1.19 to 0.10)	NR	
	Arm 2	Dexamethasone	Fatigue	ESAS Fatigue	Final: 14 Days Primary: 7 days	Baseline: 19 Followup: 13 Primary FU: 16	Baseline: Mean 5.1 (SD 2.3) Followup: Mean 4.6 (SD 1.7) Primary Followup: Mean 4.3 (SD 2.2)	Mean change from baseline: - 0.8 (SD 1.9), p=NR	Comparator: Arm 1 p=0.18	NR	
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue, 0 minutes	Borg Scale	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 3.8 (SD 3.1) Followup: Mean 2.7 (SD 3.5)	Mean change from baseline: - 1.1 (95% CI: - 1.8 to -0.4), p=Significant	NR SMD: 0 (95% CI: - 0.88 to 0.88)	NR	
	Arm 2	Fentanyl	Fatigue, 0 minutes	Borg Scale	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 2.4 (SD 1.6) Followup: Mean 1.3 (SD 1.4)	Mean change from baseline: - 1.1 (95% CI: - 1.9 to -0.3), p=Significant	NA	NR	
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue, 6 minutes	Borg Scale	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 4.6 (SD 3.2) Followup: Mean 2.8 (SD 3.3)	Mean change from baseline: - 1.9 (95% CI: -4 to 0.3), p=NS	NR SMD: 0.25 (95% CI: -0.63 to 1.13)	NR	
	Arm 2	Fentanyl	Fatigue, 6 minutes	Borg Scale	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: Mean 3.5 (SD 1) Followup: Mean 2.2 (SD 1.3)	Mean change from baseline: - 1.3 (95% CI: - 2.4 to -0.2), p=Significant	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue	Fatigue Borg Scale, at 0 minutes (before 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 1.5 (SD 1.1) Followup: Mean 1.5 (SD 1.4)	Mean change from baseline: 0 (95% CI: -0.8 to 0.8), p=NS	NR SMD: -0.70 (95% CI: -1.53 to 0.13)	NR	
	Arm 2	FPNS	Fatigue	Fatigue Borg Scale, at 0 minutes (before 6 MWT)	Final: Second Walk, 15 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 3 (SD 1) Followup: Mean 2 (SD 1.8)	Mean change from baseline: - 1 (95% CI: -1.9 to -0.1), p=Significant	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue	Fatigue Borg Scale, at 0 minutes (before 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 1.5 (SD 1.1) Followup: Mean 1.4 (SD 1.8)	Mean change from baseline: - 0.1 (95% CI: - 1.3 to 1.1), p=NS	NR SMD: -0.25 (95% CI: -1.05 to 0.55)	NR	
	Arm 2	FPNS	Fatigue	Fatigue Borg Scale, at 0 minutes (before 6 MWT)	Final: Third Walk, same day, 15 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 3 (SD 1) Followup: Mean 2.6 (SD 1.9)	Mean change from baseline: - 0.5 (95% CI: - 1.6 to 0.7), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue	Fatigue Borg Scale, at 6 minutes (after 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 3.4 (SD 2.9) Followup: Mean 2.9 (SD 2.7)	Mean change from baseline: - 0.5 (95% CI: - 1.6 to 0.7), p=NS	NR SMD: 0 (95% CI: - 0.80 to 0.80)	NR	
	Arm 2	FPNS	Fatigue	Fatigue Borg Scale, at 6 minutes (after 6 MWT)	Final: Second Walk, 20 minutes after first drug administration	Baseline: 12 Followup: 12	Baseline: Mean 3.7 (SD 2.5) Followup: Mean 3.2 (SD 2.4)	Mean change from baseline: - 0.5 (95% CI: - 1.7 to 0.8), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue	Fatigue Borg Scale, at 6 minutes (after 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 3.4 (SD 2.9) Followup: Mean 2.3 (SD 2.1)	Mean change from baseline: - 0.9 (95% CI: - 2.3 to 0.5), p=NS	NR SMD: 0.08(95% CI: -0.72 to 0.88)	NR	
	Arm 2	FPNS	Fatigue	Fatigue Borg Scale, at 6 minutes (after 6 MWT)	Final: Third Walk, same day, 20 minutes after second drug administration	Baseline: 12 Followup: 12	Baseline: Mean 3.7 (SD 2.5) Followup: Mean 2.8 (SD 2.4)	Mean change from baseline: - 0.7 (95% CI: - 2.1 to 0.6), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue, at 0 minutes (before walk)	Borg	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 1.8 (SD 1.9) Followup: Mean 1.5 (SD 1.6)	Mean change from baseline: - 0.3 (95% CI: - 1.2 to 0.7), p=NS	NR SMD: -0.18 (95% CI: -1.07 to 0.70)	NR	
	Arm 2	FBT	Fatigue, at 0 minutes (before walk)	Borg	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 1.6 (SD 1.7) Followup: Mean 1 (SD 1.1)	Mean change from baseline: - 0.6 (95% CI: - 2.1 to 1), p=NS	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue, at 6 minutes (after walk)	Borg	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 4 (SD 2.4) Followup: Mean 3.1 (SD 2.5)	Mean change from baseline: - 0.9 (95% CI: - 2.4 to 0.6), p=NS	NR SMD: -0.49 (95% CI: -1.39 to 0.403)	NR	
	Arm 2	FBT	Fatigue, at 6 minutes (after walk)	Borg	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 3.4 (SD 2.8) Followup: Mean 1.3 (SD 1.1)	Mean change from baseline: - 2.1 (95% CI: - 3.6 to -0.6), p=Significant	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Fatigue, difference between 0-6 minutes	Borg	Final: Second walk (time not specified)	Baseline: 11 Followup: 11	Baseline: Mean 2.2 (SD 3.1) Followup: Mean 1.6 (SD 2.9)	Mean change from baseline: - 0.6 (95% CI: - 2.6 to 1.4), p=NS	NR SMD: -0.37 (95% CI: -1.26 to 0.52)	NR	
	Arm 2	FBT	Fatigue, difference between 0-6 minutes	Borg	Final: Second walk (time not specified)	Baseline: 9 Followup: 9	Baseline: Mean 1.9 (SD 2.8) Followup: Mean 0.3 (SD 1)	Mean change from baseline: - 1.6 (95% CI: -4 to 0.9), p=NS	NA	NR	

CI=confidence interval; CTC=; ESAS= Edmonton Symptom Assessment Scale; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-55. Central nervous (neurocognitive measures) continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Neurocognitive testing, Arithmetic	NR	Final: After second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 88.7 (SD 42.5) Followup: Mean 84.8 (SD 47.4)	Mean change from baseline: - 3.9 (SD 27.2), p=0.56	NR SMD: -0.39 (95% CI: -1.07 to 0.29)	NR	
	Arm 2	Low dose fentanyl	Neurocognitive testing, Arithmetic	NR	Final: After second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 52.8 (SD 31.4) Followup: Mean 58.1 (SD 38.3)	Mean change from baseline: 5.2 (SD 19.6), p=0.73	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Neurocognitive testing, Reverse digits	NR	Final: After second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 4.5 (SD 2.1) Followup: Mean 3.9 (SD 2.4)	Mean change from baseline: - 0.5 (SD 1.6), p=0.36	NR SMD: -0.79 (95% CI: -1.49 to -0.09)	NR	
	Arm 2	Low dose fentanyl	Neurocognitive testing, Reverse digits	NR	Final: After second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 4.1 (SD 2.1) Followup: Mean 4.9 (SD 2.6)	Mean change from baseline: 0.8 (SD 1.7), p=0.1	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Neurocognitive testing, Tapping	NR	Final: After second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 42.1 (SD 9.9) Followup: Mean 48.9 (SD 11.2)	Mean change from baseline: 6.9 (SD 8.6), p=0.003	NR SMD: 0.47 (95% CI: -0.21 to 1.15)	NR	
	Arm 2	Low dose fentanyl	Neurocognitive testing, Tapping	NR	Final: After second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 46.4 (SD 8.4) Followup: Mean 49.8 (SD 9.1)	Mean change from baseline: 3.4 (SD 6.3), p=0.01	NA	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Neurocognitive testing, Visual	NR	Final: After second walk, not specified	Baseline: 16 Followup: 13	Baseline: Mean 5.4 (SD 1.2) Followup: Mean 5.4 (SD 1.3)	Mean change from baseline: 0 (SD 1.4), p>0.99	NR SMD: 0.09 (95% CI: -0.59 to 0.76)	NR	
	Arm 2	Low dose fentanyl	Neurocognitive testing, Visual	NR	Final: After second walk, not specified	Baseline: 18 Followup: 17	Baseline: Mean 5.7 (SD 0.8) Followup: Mean 5.5 (SD 0.9)	Mean change from baseline: - 0.1 (SD 0.9), p>0.99	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Neurocognitive testing, Arithmetic	NR	Final: Second walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 7 (95% CI: -21.5 to 35.4), p=NS	NR SMD: 0.06 (95% CI: -0.74 to 0.86)	NR	
	Arm 2	FPNS	Neurocognitive testing, Arithmetic	NR	Final: Second walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 9.9 (95% CI: - 17.6 to 37.5), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Neurocognitive testing, Arithmetic	NR	Final: Third walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 6.7 (95% CI: - 28.1 to 14.7), p=NS	NR SMD: 0.31 (95% CI: -0.49 to 1.12)	NR	
	Arm 2	FPNS	Neurocognitive testing, Arithmetic	NR	Final: Third walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 11.2 (95% CI: - 29.0 to 51.4), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Neurocognitive testing, Reverse digits	NR	Final: Second walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 0.1 (95% CI: - 1.5 to 1.3), p=NS	NR SMD: -0.05 (95% CI: -0.845 to 0.75)	NR	
	Arm 2	FPNS	Neurocognitive testing, Reverse digits	NR	Final: Second walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 0.2 (95% CI: - 1.2 to 0.9), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Neurocognitive testing, Reverse digits	NR	Final: Third walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 0.2 (95% CI: - 1.3 to 1.0), p=NS	NR SMD: -0.06 (95% CI: -0.86 to 0.74)	NR	
	Arm 2	FPNS	Neurocognitive testing, Reverse digits	NR	Final: Third walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 0.3 (95% CI: - 1.1 to 0.4), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Neurocognitive testing, Tapping	NR	Final: Second walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 1.8 (95% CI: - 0.6 to 4.1), p=NS	NR SMD: 0.22 (95% CI: -0.58 to 1.03)	NR	
	Arm 2	FPNS	Neurocognitive testing, Tapping	NR	Final: Second walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 3.3 (95% CI: - 1.5 to 8.2), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Neurocognitive testing, Tapping	NR	Final: Third walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 2.3 (95% CI: - 2.3 to 6.9), p=NS	NR SMD: 0.08 (95% CI: -0.72 to 0.88)	NR	
	Arm 2	FPNS	Neurocognitive testing, Tapping	NR	Final: Third walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 2.9 (95% CI: - 0.6 to 6.3), p=NS	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Neurocognitive testing, Visual memory	NR	Final: Second walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.5 (95% CI: - 0.7 to 1.7), p=NS	NR SMD: -0.41 (95% CI: -1.22 to 0.40)	NR	
	Arm 2	FPNS	Neurocognitive testing, Visual memory	NR	Final: Second walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 0.2 (95% CI: - 0.8 to 0.5), p=NS	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Neurocognitive testing, Visual memory	NR	Final: Third walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: 0.4 (95% CI: - 1.2 to 1.9), p=NS	NR SMD: -0.27 (95% CI: -1.08 to 0.53)	NR	
	Arm 2	FPNS	Neurocognitive testing, Visual memory	NR	Final: Third walk test, time not specified	Baseline: 12 Followup: 12	Baseline: NR Followup: NR	Mean change from baseline: - 0.2 (95% CI: - 1.0 to 0.7), p=NS	NA	NR	

CI=confidence interval; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-56. Central nervous (neurocognitive measures) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Cognitive disturbance, Grade1	NCI CTC v3	Final: 5 days	Followup: 30	0/30 (0)	NR	Ref RR: 2.91 (95% CI: 0.12 to 68.66)	NR	
	Arm 2	Midazolam	Cognitive disturbance, Grade1	NCI CTC v3	Final: 5 days	Followup: 31	1/31 (3.2)	NR	Comparator: Arm1 p=NS	NR	

CI=confidence interval; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-57. Central nervous (other adverse events) continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/ Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 2005 <sup>33</sup> Opioids vs Opioids	Arm 1	Subcutaneo us morphine	Wheezing	NRS	Final: 2 hours	Baseline: 12 Followup: 11	Baseline: NR Followup: Median 0 (SD NR), Range: 0 to 6	NR	Comparator: Not specified Difference in medians: p=NS	NR	0=no symptom, 10=worst possible symptom.
	Arm 2	Nebulized morphine	Wheezing	NRS	Final: 2 hours	Baseline: 12 Followup: 11	Baseline: NR Followup: Median 0 (SD NR), Range: 0 to 5	NR	Comparator: Not specified Difference in medians: p=NS	NR	0=no symptom, 10=worst possible symptom.

CI=confidence interval; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; SD=standard deviation



**Evidence Table D-58. Central nervous (other adverse events) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison Outcome	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kawabata, 2013 <sup>42</sup> Opioids Consciousness disturbance	Overall	Overall	Consciousness disturbance	NR	Final: NR	Followup: 95	1/95 (1.1)	NR	NR	NR	
Kawabata, 2013 <sup>42</sup> Opioids Delirium	Overall	Overall	Delirium	NR	Final: NR	Followup: 95	3/95 (3.2)	NR	NR	NR	
Navigante, 2006 <sup>43</sup> Anxiolytics vs Combination Hallucination	Arm 2	Midazolam	Hallucination, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	1/33 (3)	NR	NR RR: 0.433 (95% CI: 0.01 to 7.9)	NR	
	Arm 3	Morphine+ Midazolam	Hallucination, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics Hallucination	Arm 1	Morphine	Hallucination, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	0/35 (0)	NR	NR RR: 3.18 (95% CI: 0.13 to 75.33)	NR	
	Arm 2	Midazolam	Hallucination, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	1/33 (3)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Combination Hallucination	Arm 1	Morphine	Hallucination, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	0/35 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Morphine+ Midazolam	Hallucination, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	

CI=confidence interval; CTC=; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-59. Central nervous (sedation) continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 2005 <sup>33</sup> Opioids vs Opioids	Arm 1	Subcutaneous morphine	Sedation	NRS	Final: 2 hours	Baseline: 12 Followup: 11	Baseline: NR Followup: Median 3 (SD NR), Range: 0 to 9	NR	Comparator: Not specified Difference in medians: p=0.14	NR	0=no symptom, 10=worst possible symptom.
	Arm 2	Nebulized morphine	Sedation	NRS	Final: 2 hours	Baseline: 12 Followup: 11	Baseline: NR Followup: Median 2 (SD NR), Range: 0 to 5	NR	Comparator: Not specified Difference in medians: p=0.14	NR	0=no symptom, 10=worst possible symptom.

CI=confidence interval; CTC=; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation



**Evidence Table D-60. Central nervous (sedation) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Tian, 2016 <sup>48</sup> Corticosteroids vs Bronchodilators	Arm 2	Methylpredni solone	Somnolence	NR	Final: 1 hour	Followup: 111	0/111 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Aminophyllin e	Somnolence	NR	Final: 1 hour	Followup: 114	0/114 (0)	NR	NA	NR	
Kawabata, 2013 <sup>42</sup> Opioids	Overall	Overall	Somnolence/drowsiness	NR	Final: NR	Followup: 95	18/95 (18.9)	NR	NR	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Somnolence	NR	Final: 90 minutes	Followup: 31	15/31 (48.3)	NR	Ref RR: 1.16 (95% CI: 0.72 to 1.87)	NR	
	Arm 2	Midazolam	Somnolence	NR	Final: 90 minutes	Followup: 32	18/32 (56.3)	NR	Comparator: Arm1 p=0.53	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Somnolence, Grade2	NCI CTC v3	Final: 5 days	Followup: 30	5/30 (16.7)	NR	Ref RR: 0.77 (95% CI: 0.23 to 2.61)	NR	
	Arm 2	Midazolam	Somnolence, Grade2	NCI CTC v3	Final: 5 days	Followup: 31	4/31 (12.9)	NR	Comparator: Arm1 p=NS	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Somnolence, Grade3	NCI CTC v3	Final: 5 days	Followup: 30	1/30 (3.3)	NR	Ref RR: 0.32 (95% CI: 0.01 to 7.63)	NR	
	Arm 2	Midazolam	Somnolence, Grade3	NCI CTC v3	Final: 5 days	Followup: 31	0/31 (0)	NR	Comparator: Arm1 p=NS	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Somnolence, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	5/35 (14.3)	NR	NR RR: 1.06 (95% CI: 0.34 to 3.33)	NR	
	Arm 2	Midazolam	Somnolence, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	5/33 (15.2)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Somnolence, Grade 2 (moderate)	CTC v2	Final: 48 hours	Followup: 35	4/35 (11.4)	NR	NR RR: 0.53 (95% CI: 0.1 to 2.7)	NR	
	Arm 2	Midazolam	Somnolence, Grade 2 (moderate)	CTC v2	Final: 48 hours	Followup: 33	2/33 (6.1)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Somnolence, Grade 3 (severe)	CTC v2	Final: 48 hours	Followup: 35	2/35 (5.7)	NR	NR RR: 0.21 (95% CI: 0.01 to 4.25)	NR	
	Arm 2	Midazolam	Somnolence, Grade 3 (severe)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Anxiolytics vs Opioids+Anxiolytics	Arm 2	Midazolam	Somnolence, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	5/33 (15.2)	NR	NR RR: 0.8 (95% CI: 0.24 to 2.72)	NR	
	Arm 3	Morphine+Mi dazolam	Somnolence, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	4/33 (12.1)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Anxiolytics vs Opioids+Anxiolytics	Arm 2	Midazolam	Somnolence, Grade 2 (moderate)	CTC v2	Final: 48 hours	Followup: 33	2/33 (6.1)	NR	NR RR: 1 (95% CI: 0.15 to 6.68)	NR	
	Arm 3	Morphine+Mi dazolam	Somnolence, Grade 2 (moderate)	CTC v2	Final: 48 hours	Followup: 33	2/33 (6.1)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Anxiolytics vs Opioids+Anxiolytics	Arm 2	Midazolam	Somnolence, Grade 3 (severe)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NR RR: 3 (95% CI: 0.13 to 71.07)	NR	
	Arm 3	Morphine+Mi dazolam	Somnolence, Grade 3 (severe)	CTC v2	Final: 48 hours	Followup: 33	1/33 (3)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Opioids vs Opioids+Anxiolytics	Arm 1	Morphine	Somnolence, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	5/35 (14.3)	NR	NR RR: 0.85 (95% CI: 0.25 to 2.89)	NR	
	Arm 3	Morphine+Mi dazolam	Somnolence, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	4/33 (12.1)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Opioids+Anxiolytics	Arm 1	Morphine	Somnolence, Grade 2 (moderate)	CTC v2	Final: 48 hours	Followup: 35	4/35 (11.4)	NR	NR RR: 0.53 (95% CI: 0.1 to 2.7)	NR	
	Arm 3	Morphine+Mi dazolam	Somnolence, Grade 2 (moderate)	CTC v2	Final: 48 hours	Followup: 33	2/33 (6.1)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Opioids+Anxiolytics	Arm 1	Morphine	Somnolence, Grade 3 (severe)	CTC v2	Final: 48 hours	Followup: 35	2/35 (5.7)	NR	NR RR: 0.53 (95% CI: 0.05 to 5.58)	NR	
	Arm 3	Morphine+Mi dazolam	Somnolence, Grade 3 (severe)	CTC v2	Final: 48 hours	Followup: 33	1/33 (3)	NR	NA	NR	
Tian, 2016 <sup>48</sup> Opioids vs Bronchodilators	Arm 1	Morphine	Somnolence	NR	Final: 1 hour	Followup: 118	62/118 (52.5)	NR	NR RR: 0.01 (95% CI: 0 to 0.13)	NR	
	Arm 3	Aminophyllin e	Somnolence	NR	Final: 1 hour	Followup: 114	0/114 (0)	NR	NA	NR	

CI=confidence interval; NCI CTC= NCI Common Terminology Criteria; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-61. Equipment or drug discomfort continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Pain with subcutaneous injection	Numeric Rating Scale, 11-point	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: NR Followup: Mean 0 (SD NR), IQR: 0 to 0	NR	Ref	NR	
	Arm 2	Fentanyl	Pain with subcutaneous injection	Numeric Rating Scale, 11-point	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: NR Followup: Mean 2 (SD NR), IQR: 0.25 to 6.75	NR	Comparator: Arm 1 p=0.01	NR	

CI=confidence interval; CTC=; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation



**Evidence Table D-62. Equipment or drug discomfort categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Anxiolytics vs Opioids+Anxiolytics	Arm 2	Midazolam	Puncture site itching, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	1/33 (3)	NR	NR RR: 0.33 (95% CI: 0.01 to 7.9)	NR	
	Arm 3	Morphine+ Midazolam	Puncture site itching, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Anxiolytics vs Opioids+Anxiolytics	Arm 2	Midazolam	Puncture site redness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Morphine+ Midazolam	Puncture site redness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Puncture site itching, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	0/35 (0)	NR	NR RR: 3.18 (95% CI: 0.13 to 75.33)	NR	
	Arm 2	Midazolam	Puncture site itching, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	1/33 (3)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Puncture site redness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	1/35 (2.9)	NR	NR RR: 0.35 (95% CI: 0.01 to 8.37)	NR	
	Arm 2	Midazolam	Puncture site redness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Opioids vs Opioids+Anxiolytics	Arm 1	Morphine	Puncture site itching, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	0/35 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Morphine+ Midazolam	Puncture site itching, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Opioids+Anxiolytics	Arm 1	Morphine	Puncture site redness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	1/35 (2.9)	NR	NR RR: 0.35 (95% CI: 0.01 to 8.37)	NR	
	Arm 3	Morphine+ Midazolam	Puncture site redness, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Hardy, 2016 <sup>36</sup> Anxiolytics vs Placebo	Overall	Overall	Nasal cavity/paranasal sinus reactions, Grade 1	NCI Common Terminology Criteria for Adverse Events	Final: 14 days	Followup: 62	9/62 (14.5)	NR	NR	NR	
Hardy, 2016 <sup>36</sup>	Overall	Overall	Nasal cavity/paranasal sinus reactions, Grade 2	NCI Common Terminology Criteria for Adverse Events	Final: 14 days	Followup: 62	3/62 (4.8)	NR	NR	NR	
Anxiolytics vs Placebo	Overall	Overall	Nasal cavity/paranasal sinus reactions, Grade 3	NCI Common Terminology Criteria for Adverse Events	Final: 14 days	Followup: 62	2/62 (3.2)	NR	NR	NR	

CI=confidence interval; NCI CTC= NCI Common Terminology Criteria; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-63. Dropout due to adverse events categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Unable or unwilling to comply with the programmed follow-up visits	NCI CTC v3	Final: 90 minutes	Followup: 31	1/31 (3.2)	NR	Ref RR: 0.97 (95% CI: 0.06 to 14.82)	NR	
	Arm 2	Midazolam	Unable or unwilling to comply with the programmed follow-up visits	NCI CTC v3	Final: 90 minutes	Followup: 32	1/32 (3.2)	NR	Comparator: Arm1 p=NS	NR	
Peoples, 2016 <sup>45</sup> Anxiolytics vs Placebo	Arm 1	Placebo	Dropouts	NR	Final: 28 days	Followup: 192 (baseline)	18/192 (baseline) (9.4)	NR	NR RR: 0.5 (95% CI: 0.24 to 1.06)	NR	
	Arm 2	Buspirone	Dropouts	NR	Final: 28 days	Followup: 213 (baseline)	10/213 (baseline) (4.7)	NR	NR	NR	
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Drop out, study burden	NR	Final: 1 week	Followup: 17	Final FU: 0/17 (0)	NR	NR RR: 2.84 (95% CI: 0.12 to 65.34)	NR	
	Arm 2	Dexamethasone	Drop out, study burden	NR	Final: 1 week	Followup: 18	Final FU: 1/18 (5.6)	NR	NA	NR	
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Drop out, adverse events	NR	Final: 2 weeks	Followup: 15	Final FU: 0/15 (0)	NR	NR RR: 3.2 (95% CI: 0.14 to 72.62)	NR	
	Arm 2	Dexamethasone	Drop out, adverse events	NR	Final: 2 weeks	Followup: 14	Final FU: 1/14 (7.1)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Dropout	NR	Final: NR	Followup: 11	0/11 (0)	NR	NR RR: 3 (95% CI: 0.14 to 66.53)	NR	
	Arm 2	FBT	Dropout	NR	Final: NR	Followup: 11	1/11 (9.1)	NR	NA	NR	
Charles, 2008 <sup>34</sup> Opioids vs Placebo	Overall I	Overall	Withdrawn	NR	Final: 1 hour	Followup: 25	4/25 (16)	NR	NR	NR	

CI=confidence interval; NCI CTC= NCI Common Terminology Criteria; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-64. Dry mouth categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Anxiolytics vs Opioids+Anxiolytics	Arm 2	Midazolam	Xerostomia, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Morphine+ Midazolam	Xerostomia, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Tian, 2016 <sup>48</sup> Corticosteroids vs Bronchodilators	Arm 2	Methylpred nisolone	Xerostomia	NR	Final: 1 hour	Followup: 111	0/111 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Aminophylli ne	Xerostomia	NR	Final: 1 hour	Followup: 114	0/114 (0)	NR	NA	NR	
Navigante, 2006 <sup>43</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Xerostomia, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	1/35 (2.9)	NR	NR RR: 0.35 (95% CI: 0.01 to 8.37)	NR	
	Arm 2	Midazolam	Xerostomia, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Xerostomia, Grade2	NCI CTC v3	Final: 5 days	Followup: 30	1/30 (3.2)	NR	Ref RR: 0.32 (95% CI: 0.01 to 7.63)	NR	
	Arm 2	Midazolam	Xerostomia, Grade2	NCI CTC v3	Final: 5 days	Followup: 31	0/31 (0)	NR	Comparator: Arm1 p=NS	NR	
Tian, 2016 <sup>48</sup> Opioids vs Bronchodilators	Arm 1	Morphine	Xerostomia	NR	Final: 1 hour	Followup: 118	5/118 (4.2)	NR	NR RR: 0.09 (95% CI: 0.01 to 1.68)	NR	
	Arm 3	Aminophylli ne	Xerostomia	NR	Final: 1 hour	Followup: 114	0/114 (0)	NR	NA	NR	
Tian, 2016 <sup>48</sup> Opioids vs Corticosteroids	Arm 1	Morphine	Xerostomia	NR	Final: 1 hour	Followup: 118	5/118 (4.2)	NR	NR RR: 0.1 (95% CI: 0.01 to 1.73)	NR	
	Arm 2	Methylpred nisolone	Xerostomia	NR	Final: 1 hour	Followup: 111	0/111 (0)	NR	NA	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Navigante, 2006 <sup>43</sup> Opioids vs Opioids+Anxiolytics	Arm 1	Morphine	Xerostomia, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 35	1/35 (2.9)	NR	NR RR: 0.35 (95% CI: 0.01 to 8.37)	NR	
	Arm 3	Morphine+ Midazolam	Xerostomia, Grade 1 (mild)	CTC v2	Final: 48 hours	Followup: 33	0/33 (0)	NR	NA	NR	

CI=confidence interval; NCI CTC= NCI Common Terminology Criteria; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-65. Gastrointestinal (constipation) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Tian, 2016 <sup>48</sup> Corticosteroids vs Bronchodilators	Arm 2	Methylprednisolone	Constipation	NR	Final: 1 hour	Followup: 111	0/111 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Aminophylline	Constipation	NR	Final: 1 hour	Followup: 114	0/114 (0)	NR	NA	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Constipation, Grade2	NCI CTC v3	Final: 5 days	Followup: 30	2/30 (6.5)	NR	Ref RR: 0.19 (95% CI: 0.01 to 3.88)	NR	
	Arm 2	Midazolam	Constipation, Grade2	NCI CTC v3	Final: 5 days	Followup: 31	0/31 (0)	NR	Comparator: Arm1 p=NS	NR	
Tian, 2016 <sup>48</sup> Opioids vs Bronchodilators	Arm 1	Morphine	Constipation	NR	Final: 1 hour	Followup: 118	55/118 (46.6)	NR	NR RR: 0.01 (95% CI: 0 to 0.15)	NR	
	Arm 3	Aminophylline	Constipation	NR	Final: 1 hour	Followup: 114	0/114 (0)	NR	NA	NR	
Tian, 2016 <sup>48</sup> Opioids vs Bronchodilators	Arm 1	Morphine	Constipation	NR	Final: 1 hour	Followup: 118	55/118 (46.6)	NR	NR RR: 0.01 (95% CI: 0 to 0.15)	NR	
	Arm 2	Methylprednisolone	Constipation	NR	Final: 1 hour	Followup: 111	0/111 (0)	NR	NA	NR	

CI=confidence interval; NCI CTC= NCI Common Terminology Criteria; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-66. Gastrointestinal (diarrhea) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Diarrhea	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03	Final: 14 days	Followup: 15	0/15 (0)	NR	NR RR: 3.2 (95% CI: 0.14 to 72.62)	NR	
	Arm 2	Dexamethasone	Diarrhea	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03	Final: 14 days	Followup: 14	1/14 (7.1)	NR	NA	NR	
Pinna, 2015 <sup>46</sup> Opioids vs Placebo	Arm 1	Placebo	Diarrhea	NR	Final: NR	Followup: 11	Events: 2 (18%)	NR	NR	NR	
	Arm 2	Fentanyl citrate	Diarrhea	NR	Final: NR	Followup: 11	Events: 2 (18%)	NR	NR	NR	

CI=confidence interval; NCI CTC= NCI Common Terminology Criteria; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-67. Gastrointestinal (hemorrhage) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Gastric hemorrhage/ulcer	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03	Final: 14 days	Followup: 15	2/15 (13.3)	NR	NR	NR	
	Arm 2	Dexamethasone	Gastric hemorrhage/ulcer	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03	Final: 14 days	Followup: 14	NR/14 (NR)	NR	NR	NR	

CI=confidence interval; N=sample size; NR=not reported; SD=standard deviation



**Evidence Table D-68. Gastrointestinal (nausea) continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Bruera, 2005 <sup>33</sup> Opioids vs Opioids	Arm 1	Subcutaneo us morphine	Nausea	NRS	Final: 2 hours	Baseline: 12 Followup: 11	Baseline: NR Followup: Median 0 (SD NR), Range: 0 to 2	NR	Comparator: Not specified Difference in medians: p=NS	NR	0=no symptom, 10=worst possible symptom.
	Arm 2	Nebulized morphine	Nausea	NRS	Final: 2 hours	Baseline: 12 Followup: 11	Baseline: NR Followup: Median 0 (SD NR), Range: 0 to 7	NR	Comparator: Not specified Difference in medians: p=NS	NR	0=no symptom, 10=worst possible symptom.
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Nausea	NRS	Final: After second walk, ~20 minutes	Baseline: 16 Followup: 13	Baseline: NR Followup: NR	Mean change from baseline: -0.4 (SD 1), p=NR	NR SMD: -0.43 (95% CI: - 1.11 to -0.25)	NR	
	Arm 2	Low dose fentanyl	Nausea	NRS	Final: After second walk, ~20 minutes	Baseline: 18 Followup: 17	Baseline: NR Followup: NR	Mean change from baseline: -0.1 (SD 0.2), p=NR	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Nausea	NRS	Final: Second Walk test, ~30 minutes	Baseline: 11 Followup: 9	Baseline: NR Followup: NR	Mean change from baseline: -0.2 (SD 0.6), p=NR	NR	NR	
	Arm 2	FBT	Nausea	NRS	Final: Second Walk test, ~30 minutes	Baseline: 11 Followup: 9	Baseline: NR Followup: NR	Mean change from baseline: 0 (SD 0), p=NR	NR	NR	
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Nausea	Numeric Rating Scale, 11- point	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: NR Followup: Mean 0 (SD NR), IQR: 0 to 0	NR	Ref	NR	
	Arm 2	Fentanyl	Nausea	Numeric Rating Scale, 11- point	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: NR Followup: Mean 0 (SD NR), IQR: 0 to 0	NR	Comparator: Arm 1 p=0.32	NR	

CI=confidence interval; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-69. Gastrointestinal (nausea) categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Nausea	NRS	Final: After second walk, ~20 min after	Followup: 13	0/13 (0)	NR	NR RR: Zero events	NR	
	Arm 2	Low dose fentanyl	Nausea	NRS	Final: After second walk, ~20 min after	Followup: 17	0/17 (0)	NR	NA	NR	
Hui, 2016 <sup>39</sup> Corticosteroids vs Placebo	Arm 1	Placebo	Nausea/vomit ing	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03	Final: 14 days	Followup: 15	4/15 (26.7)	NR	NR RR: 0.12 (95% CI: 0.01 to 2.02)	NR	
	Arm 2	Dexametha sone	Nausea/vomit ing	National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03	Final: 14 days	Followup: 14	0/14 (0)	NR	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Nausea, with worse scores after 6MWT	NRS	Final: After medication administration (not specified)	Followup: 11	0/11 (0)	NR	NR RR: Zero events	NR	
	Arm 2	FBT	Nausea, with worse scores after 6MWT	NRS	Final: After medication administration (not specified)	Followup: 9	0/9 (0)	NR	NA	NR	
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Nausea (after second walk)	11-point NRS	Final: 30 minutes	Followup: 12	0/12 (0)	NR	Ref RR: Zero events	NR	
	Arm 2	FPNS	Nausea (after second walk)	11-point NRS	Final: 30 minutes	Followup: 12	0/12 (0)	NR	Comparator: Arm 1 Difference in N: p=NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2016 <sup>38</sup> Opioids vs Placebo	Arm 1	Placebo	Nausea (after third walk)	11-point NRS	Final: 30 minutes	Followup: 12	0/12 (0)	NR	Ref RR: 5 (95% CI: 0.27 to 94.34)	NR	
	Arm 2	FPNS	Nausea (after third walk)	11-point NRS	Final: 30 minutes	Followup: 12	2/12 (16.7)	NR	Comparator: Arm 1 Difference in N: p=NR	NR	

CI=confidence interval; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation; SE=standard error



**Evidence Table D-70. Pruritis continuous outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Itchiness	NRS	Final: After second walk, ~20 minutes	Baseline: 16 Followup: 13	Baseline: NR Followup: NR	Mean change from baseline: 0 (SD 0), p=NR	NR	NR	
	Arm 2	Low dose fentanyl	Itchiness	NRS	Final: After second walk, ~20 minutes	Baseline: 18 Followup: 17	Baseline: NR Followup: NR	Mean change from baseline: 0.1 (SD 0.2), p=NR	NR	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Itchiness	NRS	Second Walk test, ~30 minutes	Baseline: 11 Followup: 9	Baseline: NR Followup: NR	Mean change from baseline: 0.3 (SD 0.7), p=NR	NR	NR	
	Arm 2	FBT	Itchiness	NRS	Second Walk test, ~30 minutes	Baseline: 11 Followup: 9	Baseline: NR Followup: NR	Mean change from baseline: - 0.3 (SD 1), p=NR	NR	NR	
Hui, 2014 <sup>37</sup> Opioids vs Placebo	Arm 1	Placebo	Pruritis	Numeric Rating Scale, 11- point	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: NR Followup: Mean 0 (SD NR), IQR: 0 to 0	NR	Ref	NR	
	Arm 2	Fentanyl	Pruritis	Numeric Rating Scale, 11- point	Final: Second Walk test, not specified time	Baseline: 10 Followup: 10	Baseline: NR Followup: Mean 0 (SD NR), IQR: 0 to 0	NR	Comparator: Arm 1 p=0.15	NR	

CI=confidence interval; CTC=; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; SD=standard deviation



**Evidence Table D-71. Pruritis categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kawabata, 2013 <sup>42</sup> Opioids	Overall	Overall	Pruritis	NR	Final: NR	Followup: 95	3/95 (3.2)	NR	NR	NR	
Kawabata, 2013 <sup>42</sup> Opioids	Overall	Overall	Urinary retention	NR	Final: NR	Followup: 95	1/95 (1.1)	NR	NR	NR	
Navigante, 2010 <sup>44</sup> Opioids vs Anxiolytics	Arm 1	Morphine	Pruritus, Grade2	NCI CTC v3	Final: 5 days	Followup: 30	1/30 (3.2)	NR	Ref RR: 0.32 (95% CI: 0.01 to 7.63)	NR	
	Arm 2	Midazolam	Pruritus, Grade2	NCI CTC v3	Final: 5 days	Followup: 31	0/31 (0)	NR	Comparator: Arm1 p=NS	NR	
Hui, 2019 <sup>41</sup> Opioids vs Opioids	Arm 1	High dose fentanyl	Itchiness	NRS	Final: After second walk, ~20 min after	Followup: 13	0/13 (0)	NR	NR RR: 0.43 (95% CI: 0.02 to 9.74)	NR	
	Arm 2	Low dose fentanyl	Itchiness	NRS	Final: After second walk, ~20 min after	Followup: 17	1/17 (5.9)	NR	NA	NR	
Hui, 2017 <sup>40</sup> Opioids vs Placebo	Arm 1	Placebo	Itchiness, with worse scores after 6MWT	NRS	Final: After medication administration (not specified)	Followup: 11	2/11 (18.2)	NR	NR RR: 0.24 (95% CI: 0.01 to 4.44)	NR	
	Arm 2	FBT	Itchiness, with worse scores after 6MWT	NRS	Final: After medication administration (not specified)	Followup: 9	0/9 (0)	NR	NA	NR	

CI=confidence interval; CTC=; FBT= fentanyl buccal tablet; FPNS= fentanyl pectin nasal spray; FU=follow-up; N=sample size; NCI CTC= NCI Common Terminology Criteria; NR=not reported; NRS=Numerical Rating Scale; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation; SE=standard error



**Evidence Table D-72. Urinary retention categorical outcomes for studies comparing pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Kawabata, 2013 <sup>42</sup> Opioids	Overall	Overall	Urinary retention	NR	Final: NR	Followup: 95	1/95 (1.1)	NR	NR	NR	

n=number of patients with event; N=sample size; NR=not reported



**Evidence Table D-73. Anxiety continuous outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Anxiety	Line Analogue Rating	Final: 4 hours Primary: 4 hours	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Median change from baseline: 2 (SD NR), p=NR	Comparator: Between all arms p=0.022	NR	Not specified when participants dropped out of study.
	Arm 3	Acupuncture+ Morphine	Anxiety	Line Analogue Rating	Final: 4 hours Primary: 4 hours	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Median change from baseline: 1.4 (SD NR), p=NR	Comparator: Between all arms p=0.022	NR	Not specified when participants dropped out of study.
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Anxiety	Line Analogue Rating	Final: 14 days	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Median change from baseline: 0.3 (SD NR), p=NR	Comparator: Between all arms p=0.386	NR	
	Arm 3	Acupuncture+ Morphine	Anxiety	Line Analogue Rating	Final: 14 days	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Median change from baseline: 0.4 (SD NR), p=NR	Comparator: Between all arms p=0.386	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Anxiety	HAD	Final: 14 days	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Mean change from baseline: - 0.6 (SD 3.2), p=NR	Comparator: Between all arms p=0.171 SMD: -0.10 (95% CI: -0.49to 0.29)	NR	Possible within arm comparison p=0.676, but unable to confirm from text or table. Interaction p=0.895, but unable to confirm what this refers to.
	Arm 3	Acupuncture+ Morphine	Anxiety	HAD	Final: 14 days	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Mean change from baseline: - 0.9 (SD 2.7), p=NR	Comparator: Between all arms p=0.171	NR	Possible within arm comparison p=0.676, but unable to confirm from text or table. Interaction p=0.895, but unable to confirm what this refers to.



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Anxiety	Line Analogue Rating	Final: 4 hours Primary: 4 hours	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Median change from baseline: 2 (SD NR), p=NR	Comparator: Between all arms p=0.022	NR	Not specified when participants dropped out of study.
	Arm 2	Morphine	Anxiety	Line Analogue Rating	Final: 4 hours Primary: 4 hours	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Median change from baseline: 0.1 (SD NR), p=NR	Comparator: Between all arms p=0.022	NR	Not specified when participants dropped out of study.
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Anxiety	Line Analogue Rating	Final: 14 days	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Median change from baseline: 0.3 (SD NR), p=NR	Comparator: Between all arms p=0.386	NR	
	Arm 2	Morphine	Anxiety	Line Analogue Rating	Final: 14 days	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), p=NR	Comparator: Between all arms p=0.386	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Anxiety	HAD	Final: 14 days	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Mean change from baseline: - 0.6 (SD 3.2), p=NR	Comparator: Between all arms p=0.171 SMD: 0.13 (95% CI: -0.28 to 0.539)	NR	Possible within arm comparison p=0.676, but unable to confirm from text or table. Interaction p=0.895, but unable to confirm what this refers to.
	Arm 2	Morphine	Anxiety	HAD	Final: 14 days	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Mean change from baseline: - 0.2 (SD 3.1), p=NR	Comparator: Between all arms p=0.171	NR	Possible within arm comparison p=0.676, but unable to confirm from text or table. Interaction p=0.895, but unable to confirm what this refers to.



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Anxiety	Line Analogue Rating	Final: 4 hours Primary: 4 hours	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Median change from baseline: 0.1 (SD NR), p=NR	Comparator: Between all arms p=0.022	NR	Not specified when participants dropped out of study.
	Arm 3	Acupuncture+ Morphine	Anxiety	Line Analogue Rating	Final: 4 hours Primary: 4 hours	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Median change from baseline: 1.4 (SD NR), p=NR	Comparator: Between all arms p=0.022	NR	Not specified when participants dropped out of study.
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Anxiety	Line Analogue Rating	Final: 14 days	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), p=NR	Comparator: Between all arms p=0.386	NR	
	Arm 3	Acupuncture+ Morphine	Anxiety	Line Analogue Rating	Final: 14 days	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Median change from baseline: 0.4 (SD NR), p=NR	Comparator: Between all arms p=0.386	NR	
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Anxiety	HAD	Final: 14 days	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Mean change from baseline: - 0.2 (SD 3.1), p=NR	Comparator: Between all arms p=0.171 SMD: -0.24 (95% CI: -0.64 to 0.16)	NR	Possible within arm comparison p=0.676, but unable to confirm from text or table. Interaction p=0.895, but unable to confirm what this refers to.
	Arm 3	Acupuncture+ Morphine	Anxiety	HAD	Final: 14 days	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Mean change from baseline: - 0.9 (SD 2.7), p=NR	Comparator: Between all arms p=0.171	NR	Possible within arm comparison p=0.676, but unable to confirm from text or table. Interaction p=0.895, but unable to confirm what this refers to.

CI=confidence interval; FU=follow-up; HAD= Hospital Anxiety and Depression Scale; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-74. Breathlessness continuous outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Dyspnea	VAS	Final: 14 days	Baseline: 57 Followup: 49	Baseline: Median 6.3 (SD NR), Range: 4 to 9 Followup: NR	Mean change from baseline: - 2 (SD 2.75), p=NR	Comparator: Between all arms p=0.142 SMD: 0.08 (95% CI: -0.31 to 0.47)	NR	Possible within arm comparison p=0.005, but unable to confirm from text or table. Interaction p=0.668, but unable to confirm what this refers to.
	Arm 3	Acupuncture+ Morphine	Dyspnea	VAS	Final: 14 days	Baseline: 56 Followup: 51	Baseline: Median 6.4 (SD NR), Range: 4.1 to 8.6 Followup: NR	Mean change from baseline: - 1.79 (SD 2.32), p=NR	Comparator: Between all arms p=0.142	NR	Possible within arm comparison p=0.005, but unable to confirm from text or table. Interaction p=0.668, but unable to confirm what this refers to.
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Dyspnea	Borg scale	Final: 4 hours Primary: 4 hours	Baseline: 57 Followup: 49 Primary FU: Not specified	Baseline: NR Followup: NR	Median change from baseline: - 1 (SD NR), p=NR	Comparator: Between all arms p=0.247	NR	Not specified when participants dropped out of study.
	Arm 3	Acupuncture+ Morphine	Dyspnea	Borg scale	Final: 4 hours Primary: 4 hours	Baseline: 56 Followup: 51 Primary FU: Not specified	Baseline: NR Followup: NR	Median change from baseline: - 1 (SD NR), p=NR	Comparator: Between all arms p=0.247	NR	Not specified when participants dropped out of study.
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Dyspnea	Borg scale	Final: 14 days	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Median change from baseline: - 1 (SD NR), p=NR	Comparator: Between all arms p=0.01	NR	
	Arm 3	Acupuncture+ Morphine	Dyspnea	Borg scale	Final: 14 days	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), p=NR	Comparator: Between all arms p=0.01	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Dyspnea	VAS	Final: 14 days	Baseline: 57 Followup: 49	Baseline: Median 6.3 (SD NR), Range: 4 to 9 Followup: NR	Mean change from baseline: - 2 (SD 2.75), p=NR	Comparator: Between all arms p=0.142 SMD: 0.16 (95% CI: -0.25 to 0.56)	NR	Possible within arm comparison p=0.005, but unable to confirm from text or table. Interaction p=0.668, but unable to confirm what this refers to.
	Arm 2	Morphine	Dyspnea	VAS	Final: 14 days	Baseline: 60 Followup: 45	Baseline: Median 6.7 (SD NR), Range: 4 to 8.6 Followup: NR	Mean change from baseline: - 1.61 (SD 2.08), p=NR	Comparator: Between all arms p=0.142	NR	Possible within arm comparison p=0.005, but unable to confirm from text or table. Interaction p=0.668, but unable to confirm what this refers to.
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Dyspnea	Borg scale	Final: 4 hours Primary: 4 hours	Baseline: 57 Followup: 49 Primary FU: Not specified	Baseline: NR Followup: NR	Median change from baseline: - 1 (SD NR), p=NR	Comparator: Between all arms p=0.247	NR	Not specified when participants dropped out of study.
	Arm 2	Morphine	Dyspnea	Borg scale	Final: 4 hours Primary: 4 hours	Baseline: 60 Followup: 45 Primary FU: Not specified	Baseline: NR Followup: NR	Median change from baseline: - 1 (SD NR), p=NR	Comparator: Between all arms p=0.247	NR	Not specified when participants dropped out of study.
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Dyspnea	Borg scale	Final: 14 days	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Median change from baseline: - 1 (SD NR), p=NR	Comparator: Between all arms p=0.01	NR	
	Arm 2	Morphine	Dyspnea	Borg scale	Final: 14 days	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), p=NR	Comparator: Between all arms p=0.01	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Dyspnea	VAS	Final: 14 days	Baseline: 60 Followup: 45	Baseline: Median 6.7 (SD NR), Range: 4 to 8.6 Followup: NR	Mean change from baseline: - 1.61 (SD 2.08), p=NR	Comparator: Between all arms p=0.142 SMD: -0.08 (95% CI: -0.48 to 0.32)	NR	Possible within arm comparison p=0.005, but unable to confirm from text or table. Interaction p=0.668, but unable to confirm what this refers to.
	Arm 3	Acupuncture+ Morphine	Dyspnea	VAS	Final: 14 days	Baseline: 56 Followup: 51	Baseline: Median 6.4 (SD NR), Range: 4.1 to 8.6 Followup: NR	Mean change from baseline: - 1.79 (SD 2.32), p=NR	Comparator: Between all arms p=0.142	NR	Possible within arm comparison p=0.005, but unable to confirm from text or table. Interaction p=0.668, but unable to confirm what this refers to.
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Dyspnea	Borg scale	Final: 4 hours Primary: 4 hours	Baseline: 60 Followup: 45 Primary FU: Not specified	Baseline: NR Followup: NR	Median change from baseline: - 1 (SD NR), p=NR	Comparator: Between all arms p=0.247	NR	Not specified when participants dropped out of study.
	Arm 3	Acupuncture+ Morphine	Dyspnea	Borg scale	Final: 4 hours Primary: 4 hours	Baseline: 56 Followup: 51 Primary FU: Not specified	Baseline: NR Followup: NR	Median change from baseline: - 1 (SD NR), p=NR	Comparator: Between all arms p=0.247	NR	Not specified when participants dropped out of study.
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Dyspnea	Borg scale	Final: 14 days	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), p=NR	Comparator: Between all arms p=0.01	NR	
	Arm 3	Acupuncture+ Morphine	Dyspnea	Borg scale	Final: 14 days	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Median change from baseline: 0 (SD NR), p=NR	Comparator: Between all arms p=0.01	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Gottlieb, 2020 <sup>49</sup> Usual care vs Education+Medicati on adjustment	Arm 1	Control	Mean change in dyspnea	EORTC QLQC30, dyspnea	Final: 25 weeks	Baseline: 57 Final: 37	Baseline: Mean 27.5 (SD 29) Final: NR	Mean change from baseline: 2.7 (SD 28.7), p=NR	Comparator: Ref	NR	
	Arm 2	Intervention	Mean change in dyspnea	EORTC QLQC30, dyspnea	Final: 25 weeks	Baseline: 56 Final: 40	Baseline: Mean 37.5 (SD 29.9) Final: NR	Mean change from baseline: 0 (SD 34.6), p=NR	Comparator: Arm1 Difference in mean: -2.7 (95% CI: -17.2 to 11.8) p=0.71 SMD: -0.08 (95% CI: -0.53 to 0.36)	NR	
Gottlieb, 2020 <sup>49</sup> Usual care vs Education+Medicati on adjustment	Arm 1	Control	Mean change in dyspnea	LC13- dyspnea	Final: 25 weeks	Baseline: 55 Final: 34	Baseline: Mean 28.5 (SD 21.2) Final: NR	Mean change from baseline: 0.9 (SD 22.8), p=NR	Comparator: Ref	NR	
	Arm 2	Intervention	Mean change in dyspnea	LC13- dyspnea	Final: 25 weeks	Baseline: 54 Final: 38	Baseline: Mean 26.9 (SD 23) Final: NR	Mean change from baseline: 1.2 (SD 20.6), p=NR	Comparator: Arm1 Difference in mean: 0.3 (95% CI: -10, 10.4) p=0.97 SMD: 0.01 (95% CI: -0.45 to 0.48)	NR	

CI=confidence interval; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference; VAS=Visual Analogue Scale



**Evidence Table D-75. Breathlessness categorical outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within- Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	≥1.5 VAS dyspnea reduction	VAS	Primary: 4 hours	Primary FU: 57	Primary: 42/57 (74)	p=NR	Ref RR: 0.9 (95% CI: 0.7 to 1.14)	NR	
	Arm 3	Acupuncture+ Morphine	≥1.5 VAS dyspnea reduction	VAS	Primary: 4 hours	Primary FU: 56	Primary: 37/56 (66)	p=NR	Comparator: Arm2 p=0.5	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	≥1.5 VAS dyspnea reduction	VAS	Primary: 4 hours	Primary FU: 57	Primary: 42/57 (74)	p=NR	Ref RR: 0.81 (95% CI: 0.63 to 1.05)	NR	
	Arm 2	Morphine	≥1.5 VAS dyspnea reduction	VAS	Primary: 4 hours	Primary FU: 60	Primary: 36/60 (60)	p=NR	Comparator: Arm1 p=0.12	NR	
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	≥1.5 VAS dyspnea reduction	VAS	Primary: 4 hours	Primary FU: 60	Primary: 36/60 (60)	p=NR	Comparator: Arm1 p=0.12 RR: 1.1 (95% CI: 0.83 to 1.46)	NR	
	Arm 3	Acupuncture+ Morphine	≥1.5 VAS dyspnea reduction	VAS	Primary: 4 hours	Primary FU: 56	Primary: 37/56 (66)	p=NR	Comparator: Arm2 p=0.5	NR	

CI=confidence interval; FU=follow-up; HAD= Hospital Anxiety and Depression Scale; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; RR=relative risk; SD=standard deviation; VAS=Visual Analogue Scale



**Evidence Table D-76. Patient reported functional status continuous outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Gottlieb, 2020 <sup>49</sup> Acupuncture vs Combination	Arm 1	Control	Mean change in functional status	EORTC QLQC30, physical functionin g	Final: 25 weeks	Baseline: 57 Final: 37	Baseline: Mean 76 (SD 24.9) Final: NR	Mean change from baseline: -2.5 (SD 24.5), p=NR	Comparator: Ref	NR	
	Arm 2	Intervention	Mean change in functional status	EORTC QLQC30, physical functionin g	Final: 25 weeks	Baseline: 56 Final: 40	Baseline: Mean 75.7 (SD 19.5) Final: NR	Mean change from baseline: -5.4 (SD 16.6), p=NR	Comparator: Arm1 Difference in mean : -2.9 (95% CI: -12.3 to 6.6) p=0.55 SMD: -0.14 (95% CI: -0.59 to 0.31)	NR	

CI=confidence interval; EORTC QLQC30= European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30; N=sample size; NR=not reported; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-77. Quality of life continuous outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Quality of life	EORTC QLQ	Final: 14 days	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Mean change from baseline: 7.25 (SD 26.15), p=NR	Comparator: Between all arms p=0.009 SMD: -0.29 (95% CI: -0.68 to 0.10)	NR	Possible within arm comparison p=0.186, but unable to confirm from text or table. Interaction p=0.539, but unable to confirm what this refers to.
	Arm 3	Acupuncture+ Morphine	Quality of life	EORTC QLQ	Final: 14 days	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Mean change from baseline: 0.91 (SD 16.69), p=NR	Comparator: Between all arms p=0.009	NR	Possible within arm comparison p=0.186, but unable to confirm from text or table. Interaction p=0.539, but unable to confirm what this refers to.
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Quality of life	EORTC QLQ	Final: 14 days	Baseline: 57 Followup: 49	Baseline: NR Followup: NR	Mean change from baseline: 7.25 (SD 26.15), p=NR	Comparator: Between all arms p=0.009 SMD: -0.53 (95% CI: -0.94 to -0.12)	NR	Possible within arm comparison p=0.186, but unable to confirm from text or table. Interaction p=0.539, but unable to confirm what this refers to.
	Arm 2	Morphine	Quality of life	EORTC QLQ	Final: 14 days	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Mean change from baseline: - 5.49 (SD 21.46), p=NR	Comparator: Between all arms p=0.009	NR	Possible within arm comparison p=0.186, but unable to confirm from text or table. Interaction p=0.539, but unable to confirm what this refers to.
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Quality of life	EORTC QLQ	Final: 14 days	Baseline: 60 Followup: 45	Baseline: NR Followup: NR	Mean change from baseline: - 5.49 (SD 21.46), p=NR	Comparator: Between all arms p=0.009 SMD: 0.34 (95% CI: -0.07 to 0.74)	NR	Possible within arm comparison p=0.186, but unable to confirm from text or table. Interaction p=0.539, but unable to confirm what this refers to.
	Arm 3	Acupuncture+ Morphine	Quality of life	EORTC QLQ	Final: 14 days	Baseline: 56 Followup: 51	Baseline: NR Followup: NR	Mean change from baseline: 0.91 (SD 16.69), p=NR	Comparator: Between all arms p=0.009	NR	Possible within arm comparison p=0.186, but unable to confirm from text or table. Interaction p=0.539, but unable to confirm what this refers to.



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Gottlieb, 2020 <sup>49</sup> Usual care vs Education+Medi cation adjustment	Arm 1	Control	Mean change in QOL	EORTC QLQC30, Global Health Status	Final: 25 weeks	Baseline: 57 Final: 34	Baseline: Mean 60.2 (SD 26.4) Final: NR	Mean change from baseline: -4.4 (SD 27.1), p=NR	Comparator: Ref	NR	
	Arm 2	Intervention	Mean change in QOL	EORTC QLQC30, Global Health Status	Final: 25 weeks	Baseline: 55 Final: 40	Baseline: Mean 57.4 (SD 23.1) Final: NR	Mean change from baseline: 1.3 (SD 27.7), p=NR	Comparator: Arm1 Difference in mean : 5.7 (95% CI: -7.1 to 18.4) p=0.38 SMD: 0.21 (95% CI: -0.25 to 0.67)	NR	

CI=confidence interval; EORTC QLQ-C30= European Organization for Research and Treatment Quality of Life Questionnaire; FU=follow-up; N=sample size; NR=not reported; NS=non-significant; p=p-value; p=p-value; SD=standard deviation; SMD=standardized mean difference



**Evidence Table D-78. Clinical objective measures continuous outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	FEV1	NA	NR	Baseline: 57 Followup: NR	Baseline: Median 1.4 (SD NR), Range: 0.4 to 3.5 Followup: NR	p=NS	NR	NR	
	Arm 3	Acupuncture+ Morphine	FEV1	NA	NR	Baseline: 56 Followup: NR	Baseline: Median 1.4 (SD NR), Range: 0.5 to 2.5 Followup: NR	p=NS	NR	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	PEFR	NA	NR	Baseline: 57 Followup: NR	Baseline: Median 204 (SD NR), Range: 24 to 504 Followup: NR	p=NS	NR	NR	
	Arm 3	Acupuncture+ Morphine	PEFR	NA	NR	Baseline: 56 Followup: NR	Baseline: Median 204 (SD NR), Range: 78 to 510 Followup: NR	p=NS	NR	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	FEV1	NA	NR	Baseline: 57 Followup: NR	Baseline: Median 1.4 (SD NR), Range: 0.4 to 3.5 Followup: NR	p=NS	NR	NR	
	Arm 2	Morphine	FEV1	NA	NR	Baseline: 60 Followup: NR	Baseline: Median 1.2 (SD NR), Range: 0.4 to 2.8 Followup: NR	p=NS	NR	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	PEFR	NA	NR	Baseline: 57 Followup: NR	Baseline: Median 204 (SD NR), Range: 24 to 504 Followup: NR	p=NS	NR	NR	
	Arm 2	Morphine	PEFR	NA	NR	Baseline: 60 Followup: NR	Baseline: Median 171 (SD NR), Range: 48 to 471 Followup: NR	p=NS	NR	NR	



Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within- Group Difference	Between- Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	FEV1	NA	NR	Baseline: 60 Followup: NR	Baseline: Median 1.2 (SD NR), Range: 0.4 to 2.8 Followup: NR	p=NS	NR	NR	
	Arm 3	Acupuncture+ Morphine	FEV1	NA	NR	Baseline: 56 Followup: NR	Baseline: Median 1.4 (SD NR), Range: 0.5 to 2.5 Followup: NR	p=NS	NR	NR	
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	PEFR	NA	NR	Baseline: 60 Followup: NR	Baseline: Median 171 (SD NR), Range: 48 to 471 Followup: NR	p=NS	NR	NR	
	Arm 3	Acupuncture+ Morphine	PEFR	NA	NR	Baseline: 56 Followup: NR	Baseline: Median 204 (SD NR), Range: 78 to 510 Followup: NR	p=NS	NR	NR	

FEV1=forced expiratory volume in one second; N=sample size; NA=not available; NR=not reported; NS=nonsignificant; p=p-value; PEFR= peak expiratory flow rate; SD=standard deviation



**Evidence Table D-79. Respiratory continuous outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between- Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Respiratory rate	NA	NR	Baseline: 57 Followup: NR	Baseline: NR Followup: NR	p=NS	NR	NR	
	Arm 3	Acupuncture+Morphine	Respiratory rate	NA	NR	Baseline: 56 Followup: NR	Baseline: NR Followup: NR	p=NS	NR	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Respiratory rate	NA	NR	Baseline: 57 Followup: NR	Baseline: NR Followup: NR	p=NS	NR	NR	
	Arm 2	Morphine	Respiratory rate	NA	NR	Baseline: 60 Followup: NR	Baseline: NR Followup: NR	p=NS	NR	NR	
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Respiratory rate	NA	NR	Baseline: 60 Followup: NR	Baseline: NR Followup: NR	p=NS	NR	NR	
	Arm 3	Acupuncture+Morphine	Respiratory rate	NA	NR	Baseline: 56 Followup: NR	Baseline: NR Followup: NR	p=NS	NR	NR	

N=sample size; NA=not available; NR=not reported; NS=nonsignificant; p=p-value; SD=standard deviation



**Evidence Table D-80. Gastrointestinal (constipation) outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Constipation	NR	Final: 14 days	Followup: 57	NR/57 (NR)	NR	NR	NR	
	Arm 3	Acupuncture+ Morphine	Constipation	NR	Final: 14 days	Followup: 56	19/56 (33)	NR	NR	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Constipation	NR	Final: 14 days	Followup: 57	NR/57 (NR)	NR	NR	NR	
	Arm 2	Morphine	Constipation	NR	Final: 14 days	Followup: 60	NR/60 (NR)	NR	NR	NR	
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Constipation	NR	Final: 14 days	Followup: 60	NR/60 (NR)	NR	NR	NR	
	Arm 3	Acupuncture+ Morphine	Constipation	NR	Final: 14 days	Followup: 56	19/56 (33)	NR	NR	NR	

N=sample size; NA=not available; NR=not reported; NS=nonsignificant; p=p-value; SD=standard deviation



**Evidence Table D-81. Equipment or drug discomfort categorical outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome, n/N (%)	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids vs Combination	Overall	Overall	Irritation from acupuncture site dressing	NR	Final: 14 days	Followup: 57	2/57 (3.5)	NR	NR	NR	

N=sample size; NA=not available; NR=not reported; NS=nonsignificant; p=p-value; SD=standard deviation



**Evidence Table D-82. Dropout due to adverse events categorical outcomes for studies comparing combination nonpharmacological and pharmacological interventions for treating breathlessness in advanced cancer patients**

Author, Year Intervention Comparison	Arm	Treatment	Outcome Definition	Tool/Unit	Followup	N	Outcome	Within-Group Difference	Between-Group Difference	Adjusted Factors	Comments
Minchom, 2016 <sup>50</sup> Acupuncture vs Combination	Arm 1	Acupuncture	Dropout, not tolerating morphine	NR	Final: 14 days	Followup: 57	0/0 (0)	NR	NR RR: Zero events	NR	
	Arm 3	Acupuncture+ Morphine	Dropout, not tolerating morphine	NR	Final: 14 days	Followup: 56	0/0 (0)	NR	NA	NR	
Minchom, 2016 <sup>50</sup> Acupuncture vs Opioids	Arm 1	Acupuncture	Dropout, not tolerating morphine	NR	Final: 14 days	Followup: 57	0/0 (0)	NR	NR RR: 2.85 (95% CI: 0.12 to 68.62)	NR	
	Arm 2	Morphine	Dropout, not tolerating morphine	NR	Final: 14 days	Followup: 60	1/60 (1.67)	NR	NA	NR	
Minchom, 2016 <sup>50</sup> Opioids vs Combination	Arm 2	Morphine	Dropout, not tolerating morphine	NR	Final: 14 days	Followup: 60	1/60 (1.67)	NR	NR RR: 0.36 (95% CI: 0.01 to 8.58)	NR	
	Arm 3	Acupuncture+ Morphine	Dropout, not tolerating morphine	NR	Final: 14 days	Followup: 56	0/0 (0)	NR	NA	NR	

N=sample size; NA=not available; NR=not reported; NS=nonsignificant; p=p-value; RR=relative risk; SD=standard deviation



**Evidence Table D-83. Risk of bias assessment for randomized clinical trials comparing nonpharmacological interventions**

<b>Author, Year</b>	<b>Domain 1: Randomization Process</b>	<b>Domain 2: Deviations Intended Interventions (Effect of Assignment to Intervention)</b>	<b>Domain 2: Deviations Intended Interventions (Effect of Adhering to Intervention)</b>	<b>Domain 3: Missing Outcome Data</b>	<b>Domain 4: Measurement of the Outcome</b>	<b>Domain 5: Selection of the Reported Result</b>	<b>Final Assessment</b>
Booth, 1996 <sup>1</sup>	Some concerns	Some concerns	NA	Low risk	Low risk	Some concerns	Some concerns
Bordeleau, 2003 <sup>2</sup>	Some concerns	Some concerns	NA	Some concerns	Some concerns	Low risk	Some concerns
Bruera, 1993 <sup>3</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Some concerns	Some concerns
Bruera, 2003 <sup>4</sup>	Low risk	Some concerns	NA	Low risk	Low risk	Some concerns	Some concerns
Chan, 2011 <sup>5</sup>	High risk	Some concerns	NA	High risk	Low risk	Low risk	High risk
Corner, 1996 <sup>6</sup>	Some concerns	Some concerns	NA	High risk	Some concerns	Some concerns	High risk
Dhillon, 2017 <sup>7</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
Dogan, 2019 <sup>8</sup>	Some concerns	Some concerns	NA	Low risk	Low risk	Low risk	Some concerns
Farquhar, 2014 <sup>9</sup>	Low risk	High risk	NA	Low risk	Low risk	Low risk	High risk
Henke, 2014 <sup>10</sup>	High risk	High risk	NA	High risk	Low risk	Low risk	High risk
Hui, 2013 <sup>11</sup>	Some concerns	NA	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Hwang, 2012 <sup>12</sup>	Some concerns	Some concerns	NA	Low risk	Low risk	Some concerns	Some concerns



<b>Author, Year</b>	<b>Domain 1: Randomization Process</b>	<b>Domain 2: Deviations Intended Interventions (Effect of Assignment to Intervention)</b>	<b>Domain 2: Deviations Intended Interventions (Effect of Adhering to Intervention)</b>	<b>Domain 3: Missing Outcome Data</b>	<b>Domain 4: Measurement of the Outcome</b>	<b>Domain 5: Selection of the Reported Result</b>	<b>Final Assessment</b>
Kako, 2018 <sup>13</sup>	Some concerns	Low risk	NA	Low risk	Some concerns	Low risk	Some concerns
Ligibel, 2016 <sup>14</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
McMillan, 2007 <sup>15</sup>	Some concerns	Some concerns	NA	Some concerns	Some concerns	Low risk	Some concerns
Molassiotis, 2015 <sup>16</sup>	Some concerns	NA	High risk	High risk	Some concerns	Some concerns	High risk
Moore, 2002 <sup>17</sup>	Some concerns	Some concerns	NA	High risk	Some concerns	Some concerns	High risk
Mosher, 2019 <sup>18</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
Nakano, 2020 <sup>19</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Nava, 2013 <sup>20</sup>	Low risk	Some concerns	NA	Low risk	Some concerns	Low risk	Some concerns
Philip, 2006 <sup>21</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
Ramirez, 2018 <sup>22</sup>	Some concerns	Some concerns	NA	Low risk	Some concerns	Some concerns	Some concerns
Rutkowska, 2019 <sup>23</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
Ting, 2020 <sup>24</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns



<b>Author, Year</b>	<b>Domain 1: Randomization Process</b>	<b>Domain 2: Deviations Intended Interventions (Effect of Assignment to Intervention)</b>	<b>Domain 2: Deviations Intended Interventions (Effect of Adhering to Intervention)</b>	<b>Domain 3: Missing Outcome Data</b>	<b>Domain 4: Measurement of the Outcome</b>	<b>Domain 5: Selection of The Reported Result</b>	<b>Final Assessment</b>
Vanderbyl, 2017 <sup>25</sup>	Some concerns	NA	High risk	High risk	Low risk	Some concerns	High risk
Vickers, 2005 <sup>26</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Wong, 2017 <sup>27</sup>	Some concerns	Some concerns	NA	Low risk	Some concerns	Some concerns	Some concerns
Wyatt, 2012 <sup>28</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Yorke, 2015 <sup>29</sup>	High risk	NA	High risk	High risk	Some concerns	Some concerns	High risk

NA=not applicable



**Evidence Table D-84. Risk of bias assessment for observational studies comparing nonpharmacological interventions**

Author, Year	Domain 1: Confounding	Domain 2: Patient Selection	Domain 3: Classifying Interventions	Domain 4: Deviations From Intended Interventions	Domain 5: Missing Data	Domain 6: Measurement of Outcomes	Domain 7: Selection of Reported Results	Overall Assessment
No observational studies								



Evidence Table D-85. Risk of bias assessment for randomized clinical trials comparing pharmacological interventions

Author, Year	Domain 1: Randomization Process	Domain 2: Deviations Intended Interventions (Effect of Assignment To Intervention)	Domain 2: Deviations Intended Interventions (Effect of Adhering to Intervention)	Domain 3: Missing Outcome Data	Domain 4: Measurement of the Outcome	Domain 5: Selection of the Reported Result	Final Assessment
Aabom, 2019 <sup>30</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Allard, 1999 <sup>31</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
Bruera, 1993 <sup>32</sup>	Some concerns	Low risk	NA	Low risk	High risk	Low risk	High risk
Bruera, 2005 <sup>33</sup>	Some concerns	Low risk	NA	Some concerns	Low risk	Some concerns	High risk
Charles, 2008 <sup>34</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Some concerns	High risk
Gamborg, 2013 <sup>35</sup>	Some concerns	Some concerns	NA	Low risk	Some concerns	Low risk	High risk
Hardy, 2016 <sup>36</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2014 <sup>37</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2016 <sup>38</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2016 <sup>39</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2017 <sup>40</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2019 <sup>41</sup>	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Navigante, 2006 <sup>43</sup>	Low risk	Some concerns	NA	Low risk	Some concerns	Some concerns	High risk
Navigante, 2010 <sup>44</sup>	Low risk	Some concerns	NA	Low risk	Some concerns	Some concerns	Some concerns
Peoples, 2016 <sup>45</sup>	Low risk	Low risk	NA	Some concerns	Low risk	Low risk	Some concerns
Pinna, 2015 <sup>46</sup>	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
Simon, 2016 <sup>47</sup>	Some concerns	Low risk	NA	Some concerns	High risk	High risk	High risk

NA=not applicable



Evidence Table D-86. Risk of bias assessment for observational studies comparing pharmacological interventions

Author, Year	Domain 1: Confounding	Domain 2: Patient Selection	Domain 3: Classifying Interventions	Domain 4: Deviations From Intended Interventions	Domain 5: Missing Data	Domain 6: Measurement of Outcomes	Domain 7: Selection of Reported Results	Overall Assessment
Kawabata, 2013 <sup>42</sup>	Critical	Serious	Low	No information	Moderate	Moderate	Serious	Critical
Tian, 2016 <sup>48</sup>	Serious	Moderate	Low	Moderate	Moderate	Moderate	Serious	Serious



**Evidence Table D-87. Risk of bias assessment for randomized clinical trials comparing combination of nonpharmacological and pharmacological interventions**

Author, Year	Domain 1: Randomization Process	Domain 2: Deviations Intended Interventions (Effect of Assignment to Intervention)	Domain 2: Deviations Intended Interventions (Effect of Adhering to Intervention)	Domain 3: Missing Outcome Data	Domain 4: Measurement of the Outcome	Domain 5: Selection of the Reported Result	Final Assessment
Gottlieb, 2020 <sup>49</sup>	Some concerns	Some concerns	NA	Low risk	Low risk	Low risk	Some concerns
Minchom, 2016 <sup>50</sup>	Some concerns	Low risk	NA	Some concerns	Some concerns	Low risk	Some concerns

NA=not applicable



**Evidence Table D-88. Risk of bias assessment for observational studies comparing combination of nonpharmacological and pharmacological interventions**

Author, Year	Domain 1: Confounding	Domain 2: Patient Selection	Domain 3: Classifying Interventions	Domain 4: Deviations From Intended Interventions	Domain 5: Missing Data	Domain 6: Measurement of Outcomes	Domain 7: Selection of Reported Results	Overall Assessment
No observational studies								



**Evidence Table D-89. Strength of evidence of studies that evaluate the effects of nonpharmacologic interventions**

Intervention	Key Outcome	Intervention	Number of Studies (Participants)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
Respiratory interventions	Breathlessness	Airflow vs usual care/ placebo	3 RCTs (115)	Medium	Direct	Consistent	Precise	Suspected	Moderate
	Breathlessness	Compressed air vs standard supplemental oxygen	4 RCTs (96)	Medium	Direct	Consistent	Imprecise	Suspected	Low
	Breathlessness	Bilevel ventilation vs high flow nasal cannula	1 RCT (30)	Medium	Direct	Unknown	Imprecise	Suspected	Low
	Breathlessness	Bilevel ventilation vs. standard supplemental oxygen	1 RCT (189)	Medium	Direct	Unknown	Imprecise	Suspected	Low
	Anxiety	Airflow vs placebo	1 RCT (40)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
	Exercise capacity	Compressed air vs standard supplemental oxygen	1 RCT (33)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
Behavioral and psychoeducational interventions	Breathlessness	Behavioral and psychoeducational interventions vs usual care	3 RCTs (197)	High	Direct	Inconsistent	Precise	Suspected	Low
	Health-related quality of life	Behavioral and psychoeducational interventions vs usual care	3 RCTs (197)	High	Direct	Consistent	Precise	Suspected	Low
Activity and Rehabilitation Interventions	Breathlessness	Activity and rehabilitation interventions vs activity and rehabilitation interventions or usual care	7 RCTs (227)	High	Direct	Consistent	Imprecise	Suspected	Low
	Anxiety	Activity and rehabilitation interventions vs activity and rehabilitation interventions or usual care	2 RCTs (60)	High	Direct	Inconsistent	Imprecise	Suspected	Insufficient
	Exercise capacity	Activity and rehabilitation interventions vs activity and rehabilitation interventions or usual care	3 RCTs (72)	High	Direct	Consistent	Imprecise	Suspected	Low
	Health-related quality of life	Activity and rehabilitation interventions vs activity and rehabilitation interventions or usual care	5 RCTs (188)	High	Direct	Consistent	Imprecise	Suspected	Low



	Key Outcome	Intervention	Number of Studies (Participants)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
<b>Integrative Medicine Interventions: Acupuncture</b>	Breathlessness	Acupuncture vs sham acupuncture	1 RCT (33)	Low	Direct	Unknown	Precise	Suspected	Insufficient
<b>Integrative Medicine Interventions: Acupressure/ reflexology</b>	Breathlessness	Acupressure/ reflexology versus placebo intervention or usual care or both	2 RCTs (206)	Medium	Direct	Consistent	Imprecise	Suspected	Low
	Anxiety	Acupressure/ reflexology versus placebo intervention or usual care or both	1 RCT (222)	Low	Direct	Unknown	Precise	Suspected	Insufficient
	Exercise capacity	Acupressure/ reflexology versus placebo intervention or usual care or both	1 RCT (60)	Low	Direct	Unknown	Precise	Suspected	Insufficient
	Health-related quality of life	Acupressure/ reflexology versus placebo intervention or usual care or both	2 RCTs (206)	Medium	Direct	Consistent	Precise	Suspected	Low
<b>Integrative Medicine Interventions: Music therapy</b>	Breathlessness	Music therapy vs usual care	1 RCT (40)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
	Anxiety	Music therapy vs usual care	1 RCT (40)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
<b>Multicomponent Interventions: Combined Activity and Rehabilitation and Behavioral Psychoeducational Interventions</b>	Breathlessness	Combined Activity and Rehabilitation and Behavioral Psychoeducational Interventions, vs usual care	3 RCTs (184)	High	Direct	Inconsistent	Imprecise	Suspected	Low
	Anxiety	Combined Activity and Rehabilitation and Behavioral Psychoeducational Interventions, vs usual care	3 RCTs (212)	High	Direct	Inconsistent	Imprecise	Suspected	Low
	Exercise capacity	Combined Activity and Rehabilitation and Behavioral Psychoeducational Interventions, vs usual care	1 RCT (62)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
	Health-related quality of life	Combined Activity and Rehabilitation and Behavioral Psychoeducational Interventions, vs usual care	1 RCT (62)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient



Intervention	Key Outcome	Intervention	Number of Studies (Participants)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
<b>Multicomponent Interventions: Combined Activity and Rehabilitation, Behavioral Psychoeducational, and Integrative Medicine Interventions</b>	Breathlessness	Combined Activity and Rehabilitation, Behavioral Psychoeducational, and Integrative Medicine Interventions, vs usual care	2 RCTs (100)	High	Direct	Consistent	Precise	Suspected	Low
	Anxiety	Combined Activity and Rehabilitation, Behavioral Psychoeducational, and Integrative Medicine Interventions, vs usual care	2 RCTs (99)	High	Direct	Consistent	Precise	Suspected	Low
	Health-related quality of life	Combined Activity and Rehabilitation, Behavioral Psychoeducational, and Integrative Medicine Interventions, vs usual care	2 RCTs (99)	High	Direct	Consistent	Precise	Suspected	Low
<b>Multicomponent Interventions: Combined Behavioral and Psychoeducational and Integrative Medicine Interventions</b>	Breathlessness	Behavioral and Psychoeducational and Integrative Medicine Interventions vs usual care	1 RCT (38)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
	Anxiety	Behavioral and Psychoeducational and Integrative Medicine Interventions vs usual care	1 RCT (38)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient

RCT=randomized clinical trial



**Evidence Table D-90. Strength of evidence of studies that evaluate the effects of pharmacologic interventions**

Key Outcome	Intervention	Number of Studies (Participants)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
Breathlessness	Opioids vs Placebo	6 RCT (107 participants)	Low	Direct	Consistent	Precise	Undetected	Moderate
Breathlessness	Anxiolytics vs Placebo	2 RCT (311 participants)	Medium	Direct	Consistent	Imprecise	Undetected	Low
Breathlessness	Corticosteroids vs Placebo	1 RCT (28 participants)	Low	Direct	Unknown	Imprecise	Suspected	Insufficient
Breathlessness	Opioids vs Opioids	7 RCT (132 participants)	High	Direct	Consistent	Imprecise	Suspected	Low
Breathlessness	Opioids vs Anxiolytics	2 RCT (108 participants)	Medium	Direct	Inconsistent	Imprecise	Suspected	Low
Breathlessness	Opioids vs Corticosteroids vs Bronchodilators	1 retrospective cohort (343 participants)	High	Direct	Unknown	Imprecise	Suspected	Insufficient
Anxiety	Anxiolytics vs Placebo	2 RCT (311 participants)	Medium	Direct	Consistent	Precise	Undetected	Low
Health-related quality of life	Corticosteroids vs Placebo	1 RCT (28 participants)	Low	Direct	Unknown	Imprecise	Suspected	Insufficient
Exercise capacity	Opioids vs Placebo	4 RCT (77 participants)	Low	Direct	Consistent	Precise	Undetected	Moderate

RCT=randomized clinical trial



**Evidence Table D-91. Strength of evidence of studies that evaluate the effects of combinations of nonpharmacological and pharmacological interventions, or the comparative effectiveness of nonpharmacological compared with pharmacological interventions**

Intervention	Key Outcome	Intervention	Number of Studies (Participants)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Strength of Evidence
<b>Opioid vs Acupuncture vs Opioid-acupuncture combinations</b>	Breathlessness	Opioid vs Acupuncture vs Opioid-acupuncture combinations	1 RCT (145 participants)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
	Anxiety	Opioid vs Acupuncture vs Opioid-acupuncture combinations	1 RCT (145 participants)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
	Health-related quality of life	Opioid vs Acupuncture vs Opioid-acupuncture combinations	1 RCT (145 participants)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
<b>Multimodal management of chronic obstructive pulmonary disease</b>	Breathlessness	Multimodal management of chronic obstructive pulmonary disease vs usual care	1 RCT (77participants)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient
	Health-related quality of life	Multimodal management of chronic obstructive pulmonary disease vs usual care	1 RCT (74 participants)	Medium	Direct	Unknown	Imprecise	Suspected	Insufficient

RCT=randomized clinical trial



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## Appendix E. PCORI Systematic Review Checklist

	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
Cross-Cutting Standards for PCOR	Standards for Formulating Research Questions	RQ-1	Identify gaps in evidence.	Yes	Introduction (pag 1,2)	
		RQ-2	Develop a formal study protocol.	Yes	Pre-report protocol	
		RQ-3	Identify specific populations and health decision(s) affected by the research.	Yes	Methods, page 4 and methods appendix	
	Standards for Formulating Research Questions (continued)	RQ-4	Identify and assess participant subgroups.	N/A		
		RQ-5	Select appropriate interventions and comparators.	Yes	Methods, page 4 and methods appendix	
		RQ-6	Measure outcomes that people representing the population of interest notice and care about.	Yes	Methods, page 4 and methods appendix	
	Standards Associated with Patient-Centeredness	PC-1	Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context.	Yes	TEP call	



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
	Standards Associated with Patient-Centeredness (continued)	PC-2	Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants.	N/A		
		PC-3	Use patient-reported outcomes when patients or people at risk of a condition are the best source of information for outcomes of interest.	N/A		
		PC-4	Support dissemination and implementation of study results.	N/A		Intent is to publish report and possibly a journal article with findings from the review when completed
	Standards for Data Integrity and Rigorous Analyses	IR-1	A priori, specify plans for quantitative data analysis that correspond to major aims.	Yes	Methods page 5,6	
	Standards for Data Integrity and Rigorous Analyses (continued)	IR-2	Assess data source adequacy.			
		IR-3	Describe data linkage plans, if applicable.	N/A		Standard does not apply
		IR-4	Document validated scales and tests.	Yes	Appendix D - evidence tables	



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
		IR-5	Provide sufficient information in reports to allow for assessments of the study's internal and external validity.	Yes	Appendix D - evidence tables	
		IR-6	Masking should be used when feasible.	N/A		
	Standards for Data Integrity and Rigorous Analyses (continued)	IR-7	In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.	Yes	protocol	
	Standards for Preventing and Handling Missing Data	MD-1	Describe methods to prevent and monitor missing data.	Yes	Pre-report protocol	
		MD-2	Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness.	N/A		
		MD-3	Record and report all reasons for dropout and missing data, and account for all patients in reports.	N/A		
	Standards for Preventing and Handling Missing Data (continued)	MD-4	Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation.	N/A		



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
	Standards for Heterogeneity of Treatment Effect (HTE)	HT-1	State the goals of HTE analyses, including hypotheses and the supporting evidence base.	Yes	Methods, page 6	
		HT-2	For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods.	Yes	Methods, page 6	
		HT-3	Report all prespecified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed.	Yes	Results, page 19, 42, 43 Appendix C, page C-15 through C-34	
Standards for Specific Study Designs and Methods	Standards for Data Registries	DR-1	Requirements for the design of registries.	N/A		
		DR-2	Documentation and reporting requirements of registry materials, characteristics, and bias.	N/A		
		DR-3	Adapting established registries for PCOR.	N/A		
		DR-4	Documentation requirements when using registry data.	N/A		



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
	Standards for Data Networks as Research-Facilitating Structures	DN-1	Requirements for the design and features of data networks.	N/A		
		DN-2	Selection and use of data networks.	N/A		
	Causal Inference Standards	CI-1	Specify the causal model underlying the research question (cross-cutting standard, applies to all PCOR/CER studies).	N/A		
		CI-2	Define and appropriately characterize the analysis population used to generate effect estimates.	N/A		
		CI-3	Define with the appropriate precision the timing of the outcome assessment relative to the initiation and duration of exposure.	N/A		
		CI-4	Measure potential confounders before start of exposure and report data on potential confounders with study results.	N/A		
	Causal Inference Standards (continued)	CI-5	Report the assumptions underlying the construction of propensity scores and the comparability of the resulting groups in terms of the balance of covariates and overlap.	N/A		



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
		CI-6	Assess the validity of the instrumental variable (i.e., how the assumptions are met) and report the balance of covariates in the groups created by the instrumental variable.	N/A		
	Standards for Adaptive and Bayesian Trial Designs	AT-1	Specify planned adaptations, decisional thresholds, and statistical properties of those adaptations.	N/A		Standard does not apply
		AT-2	Specify the structure and analysis plan for Bayesian adaptive randomized clinical trial designs.	N/A		Standard does not apply
	Standards for Adaptive and Bayesian Trial Designs (continued)	AT-3	Ensure that clinical trial infrastructure is adequate to support planned adaptation(s) and independent interim analyses.	N/A		Standard does not apply
		AT-4	When reporting adaptive randomized clinical trials, use the CONSORT statement, with modifications.	N/A		Standard does not apply
	Standards for Studies of Medical Tests	MT-1	Specify clinical context and key elements of the medical test.	N/A		
		MT-2	Assess the effect of factors known to affect performance and outcomes.	N/A		



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
		MT-3	Focus studies of medical tests on patient-centered outcomes, using rigorous study designs with a preference for randomized controlled trials.	N/A		
	Standards for Systematic Reviews	SR-1	Adhere to National Academy of Medicine (NAM) standards for systematic reviews of comparative effectiveness research, as appropriate.	Yes	Entire report	
	Standards on Research Designs Using Clusters	RC-1	Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or the individual level.	N/A		Standard does not apply
		RC-2	Justify the choice of cluster randomization.	N/A		Standard does not apply
		RC-3	Power and sample size estimates must use appropriate methods to account for the dependence of observations within clusters and the degrees of freedom available at the cluster level.	N/A		Standard does not apply
	Standards on Research Designs Using Clusters (continued)	RC-4	Data analyses must account for the dependence of observations within clusters regardless of its magnitude.	N/A		Standard does not apply
		RC-5	Stratified randomization should be used when feasible.	N/A		Standard does not apply



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
	Standards for Studies of Complex Interventions	SCI-1	Fully describe the intervention and comparator and define their core functions.	N/A		
		SCI-2	Specify the hypothesized causal pathways and their theoretical basis.	N/A		
	Standards for Studies of Complex Interventions (continued)	SCI-3	Specify how adaptations to the form of the intervention and comparator will be allowed and recorded.	N/A		
		SCI-4	Plan and describe a process evaluation.	N/A		
		SCI-5	Select patient outcomes informed by the causal pathway.	N/A		
	Standards for Qualitative Methods	QM-1	State the qualitative approach to research inquiry, design, and conduct.	N/A		Standard does not apply
		QM-2	Select and justify appropriate qualitative methods sampling strategy.	N/A		Standard does not apply



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
	Standards for Qualitative Methods (continued)	QM-3	Link the qualitative data analysis, interpretations, and conclusions to the study question.	N/A		Standard does not apply
		QM-5	Establish trustworthiness and credibility of qualitative research.	N/A		Standard does not apply
	Standards for Mixed Methods Research	MM-2	Specify how mixed methods are integrated across design, data sources, and/or data collection phases.	N/A		Standard does not apply
		MM-2	Select and justify appropriate mixed methods sampling strategy.	N/A		Standard does not apply
	Standards for Mixed Methods Research (continued)	MM-3	Integrate data analysis, data interpretation, and conclusions.	N/A		Standard does not apply
	Standards for Individual Participant-Level Data Meta-Analysis (IPD-MA)	IPD-1	Specify the research question(s) that will be addressed through the IPD-MA and describe the specific information it will provide that other approaches would not.	N/A		Standard does not apply
		IPD-2	Describe the proposed governance structure for the IPD-MA in the protocol and study reports.	N/A		Standard does not apply



	Standard Category	Abbreviation	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard
		IPD-3	Use systematic, reproducible methods to identify studies for inclusion in the IPD-MA.	N/A		Standard does not apply
		IPD-4	Specify the design and planned analyses of the IPD-MA in a protocol, document any changes, and report significant amendments and modifications.	N/A		Standard does not apply

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