Comparative Effectiveness Review
Number 232

Interventions for Breathlessness in Patients With Advanced Cancer

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.

Agency for Healthcare Research and Quality

Background and Purpose

Breathlessness, defined as difficulty breathing or shortness of breath, is frequent in advanced cancer[1] and often debilitating. Acute, chronic, or exertional breathlessness can reduce ability to function and participate in desired activities[2] and can be distressing for caregivers and patients. When treatment of the primary cause or comorbidities does not fully relieve symptoms or is not possible, 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.[3] 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) (2,423 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.

References

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3. 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

Full Report

Dy SM, Gupta A, Waldfogel JM, Sharma R, Zhang A, Feliciano JL, Sedhom R, Day J, Gersten RA, Davidson PM, Bass EB. Interventions for Breathlessness in Patients With Advanced Cancer. Comparative Effectiveness Review No. 232. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2015-00006-I for the Agency for Healthcare Research and Quality and the Patient-Centered Outcomes Research Institute.) AHRQ Publication No. 21-EHC024, PCORI Publication No. 2020-SR-01. Rockville, MD: Agency for Healthcare Research and Quality; November 2020.
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