Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Interventions for Breathlessness in Patients With Advanced Cancer

Draft report available for public comment from March 12, 2020 to May 4, 2020.

Research Review Citation: 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. DOI: 10.23970/AHRQEPCCER232.

Comments to Draft Report

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each draft report is posted to the EHC Program website or AHRQ website for public comment for a 45-day period. Comments can be submitted via the website, mail, or email. At the conclusion of the public comment period, authors use the commentators' comments to revise the draft report.

Comments on draft reports and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Reviewer #1 (TEP)	General Comments	Yes, the report is clinically meaningful and will be practice changing. The target audience should be oncology HCPs with an emphasis on palliative care and hospice. It would be great to have a specific focus on nurses. Yes, the key questions are appropriate and explicit.	Thank you
Reviewer #1 (TEP)	Introduction	Well written and clear	Thank you
Reviewer #1 (TEP)	Methods	Yes, clear and explicitly stated. Statistical methods are appropriate.	Thank you
Reviewer #1 (TEP)	Results	The summary of key findings tables are excellent.	Thank you
Reviewer #1 (TEP)	Discussion/ Conclusion	Yes, the findings are clear and the future research section is easily translated to new research. Since the findings for nonpharm interventions was significant it may be beneficial to have a table outlining the components of these interventions as part of the dissemination tools with the guideline.	We will pass this comment on to the guideline committee.
Reviewer #2 (TEP)	General Comments	1. Dyspnea is an important concern among patients with advanced cancer; this systematic review aims to assess the benefits and adverse effects associated with pharmacologic and non-pharmacologic therapies. The investigators should be commended on this project - it is a lot of work to retrieve the studies, put them together and interpret them. 2. The report's clinical utility is somewhat hampered by the paucity of high quality studies, combining studies with very different interventions/designs, and some issues with study interpretation. 3. The 4 questions are appropriate - but quite broad in scope.	Thank you. Note that the questions were as provided by ASCO/PCORI/AHRQ.
Reviewer #2 (TEP)	Introduction	The introduction is well written and concise.	Thank you

Reviewer #2 (TEP)	Methods	1. The eligibility criteria are somewhat restrictive and resulting in the exclusion of some relevant studies. The authors only included studies if >50% of population consists of cancer patients to ensure some degree of homogeneity; however, this significantly limits the number of included studies, excluding many studies with <50% of cancer patients even though the number of cancer patients in those studies were still larger than some of the included studies with 100% cancer patients.	1. We appreciate this concern – however, our charge from ASCO was to focus on advanced cancer patients, and ASCO and our Technical Expert Panel supported this approach. Breathlessness in patients with cancer can have unique characteristics and correlates and deserves particular consideration, versus 'lumping' data from other cardiopulmonary disease states, such as chronic obstructive pulmonary disease and congestive heart failure. We would have included information if it was presented separately, but these studies did not include information specifically for cancer patients. E.g. Higginson, et al. Lancet Respir Med. 2014 Dec;2(12):979-87 https://www.ncbi.nlm.nih.gov/pubmed/25465642 included 105 patients randomized to an integrated palliative and respiratory care service or usual care. COPD was 54% (57) of patients, and cancer was only 21% (20) patients. However, no cancer-specific outcomes were presented. So even though the number of patients met criteria, the overall results would not represent the cancer population. 1] Additionally, breathlessness in patients with cancer is closely associated with other common symptoms, such as anxiety, appetite loss, drowsiness, and fatigue.[2] Thus, focusing specifically on patients with advanced cancer provides much needed evidence in this field. [1]Reddy SK, Parsons HA, Elsayem A, Palmer JL, Bruera E. Characteristics and correlates of dyspnea in patients with advanced cancer. J Palliat Med. 2009;12(1):29-36. [2]McKenzie, Zhang L, Chan S, et al. Symptom correlates of dyspnea in advanced cancer patients using the Edmonton Symptom Assessment System. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2020;28(1):87-98.
		2. The rationale for only including patients with advanced cancer instead of only patients with cancer should be better justified. In fact, some of the included studies did not specify that they only enrolled patients with advanced cancer.	2. Advanced cancer was our charge from ASCO. All studies were checked carefully by at least 2 independent investigators that they were advanced cancer. We excluded several studies which did not specify advanced or where we could not tell -

			for example, another reviewer suggested to include Puspawati NLPD et al, Asia Pac J Oncol Nurs, 2017 (RCT, crossover design). https://www.ncbi.nlm.nih.gov/pubmed/28503650 but we double checked and excluded the study since it did not indicate ''advanced.'. This reviewer did not mention any specific studies that we included that did not specify advanced cancer.
		3. My most important concern is that the existing literature on dyspnea in advanced cancer is highly diverse in terms of patient population, intervention nature, duration and intensity, and methodologic rigour (primary outcomes, blinding, sample size etc). On several occasions, the investigators combined very heterogeneous studies, which run the risk of loss of signal and over-generalization in the conclusions. See Barnard et al. JAMA. 2017 Oct 17;318(15):1435-1436. Systematic reviews and meta-analyses are best when studies of very similar patients, interventions and designs are combined together. If studies were not similar enough, I don't think it is a good idea to lump them together for the sake of a conclusion. Instead, the studies should be reviewed individually and critically appraised. I would recommend acknowledging the paucity in data, limitations in study design and the need for more research. Below are some examples:	3. We appreciate this comment, and these decisions are a balance between combining heterogeneous studies and being able to draw some conclusions in order to inform the guideline and clinical practice. We carefully reviewed our meta-analyses again with this comment in mind. Ultimately, we have been very selective about the meta-analyses that were performed, carefully taking into consideration the heterogeneity of the studies in terms of population, intervention, and methodologic rigor. We have noted the limitations of the meta-analyses and need for studies focusing on specific breathlessness types and populations and settings more specifically in the future research section.
		a. Under compressed air vs. oxygen, the investigators combined patients who were hypoxemic and those who were non-hypoxemic together. The one study in hypoxemic patients showed signal; while the others in nonhypoxemic patients did not. This distinction is important because of the mechanism – if you are hypoxemic, oxygen may be useful. By combining all these studies together, the signal in hypoxemic patients is lost "We concluded that compressed air and supplemental oxygen did not differ in improving dyspnea". Hypoxemic and non-hypoxemic studies should not be combined.	a. We have now presented data by patients with and without hypoxemia when presenting results of compressed air vs standard supplementation oxygen, although this does not change the conclusions. Of 3 trials comparing these interventions in patients with hypoxemia, one reported that standard supplementation oxygen was more effective than compressed air, while two studies did not. We concluded that compressed air and standard supplemental oxygen did not differ in improving dyspnea, overall, or in patients with or without baseline hypoxemia.
		b. Under activity and rehabilitation interventions, it is unclear why Qigong is combined with exercise	b. Qigong is an ancient Chinese exercise and healing technique that involves meditation, controlled breathing

		therapy and respiratory training. Statement such as "we concluded that activity and rehabilitation interventions did not consistently improve dyspnea" is perhaps an overstatement. I would be more appropriate to state.	and movement exercises. So, we found it reasonable to classify it as exercise and respiratory training and our expert on the panel in integrative medicine felt this was acceptable. We have carefully reviewed this conclusion with this comment in mind and felt it was appropriate.
		c. Under complementary and alternative medicine, it seems to be overdrawn conclusion by combining acupressure, reflexology and music therapy. They have different potential mechanisms,	c. We have made sure to clarify that we did not combine music with other touch therapies (acupressure/reflexology) while extracting data or drawing conclusions. They were just 4 listed together under integrative medicine. The expert in integrative medicine on the panel felt this was acceptable.
		d. Under opioids, the studies had very different designs. Some were using opioids for treatment (e.g. Charles et al.), others were using opioids for prevention of dyspnea before exercises. I would disagree that opioids don't work because some studies demonstrated a clear pharmacologic effect and some studies had major methodologic flaws. My conclusion based on the evidence is that there the evidence is inconclusive rather than opioids are not better than placebo (see point 4).	d. We appreciate this comment and have noted more clearly throughout the report the type of breathlessness addressed (acute vs chronic vs exertional) and expanded on this in the discussion of limitations of the review. Consensus among the investigators and reviewers was that these were similar enough to combine. Four of the included RCTs are of fentanyl vs placebo evaluating exertional dyspnea after 6 minute walk tests. The Charles study, although not of exertional dyspnea related to a 6 minute walking test, was treating acute incident breathlessness over a similar period of time (10 minutes). Removing the Charles study would not change the results of the meta-analysis. There was often a clear within group difference for opioids but there was also a consistent within group difference for placebo; we have noted this important point as well in the discussion. The conclusion about effectiveness is based on the meta-analysis results and minimal clinically important difference; the methodologic flaws are considered in the strength of evidence.
		e. Combining buspirone and midazolam under the category "anxiolytics" does not make sense.	e. We appreciate that feedback. We considered both as accepted treatments for anxiety and so labeled them as anxiolytics and included them in the same sections. We agree they often treat very different patient populations or acuities and have very different pharmacologic mechanisms. Given these differences that you note, we did not conduct a meta-analysis.
		4. Statistical approach and evaluation of studies for bias appear appropriate.	4. Thank you

Reviewer #2 (TEP)	Results	1. Ultimately, the investigators stated that multiple intervention categories "did not consistently produce a clinically important improvement" when there were actually inadequate data to draw conclusions and/or the intervention categories should not be combined for interpretation. For example, under behavioural interventions, the 3 studies included had VERY different duration, intensity, and focus. My conclusion would be 1 of 3 studies examining behavioral interventions with very different designs showed some activity. There is inadequate data to reach a conclusion regarding efficacy and further research is needed. Similarly, they concluded that "opioids and anxiolytics were not effective in improving dyspnea" when there is inadequate evidence to support this conclusion. 2. The criteria for when an intervention is declared effective is unclear. For example, the authors concluded that "acupuncture/acupressure/reflexology were more effective at reducing dyspnea than usual care or sham procedures" based on 3 studies with major limitations in design quality and reporting, in addition to heterogeneity in intervention and patient population. 3. It is unclear why the Mosher study (Ref 42) which examined Acceptance-commitment therapy in lung cancer patients was singled out in its own category of "Behavioural and psychoeducational and complementary or alternative medicine interventions". 4. Under opioids, it is unclear why some studies were specifically excluded (e.g. Bruera et al. Lancet, Mazzocato et al Ann Oncol). These studies are of importance and clearly demonstrated that efficacy of morphine. Importantly, these 2 studies were using opioids for treatment and should ideally be analyzed separately from the prophylaxis studies.	1. On your comment on behavioral interventions – thank you for this; we reconsidered the evidence carefully based on your comment. Given the 3 studies with substantial sample size, and our prespecified criteria, we have kept the conclusion as is, noting that the strength of evidence is low. We have carefully considered the comments on opioids - given the large number of studies, most of which are consistent, and very small effect size that was not clinically meaningful, we draw a conclusion that they are not effective but note the uncertainty with the strength of evidence. Similarly, for anxiolytics, given two consistent studies, we conclude that they are not effective but support the uncertainty of this conclusion with the low strength of evidence. 2. Based on the comments from other reviewers including the integrative medicine expert, we have now only combined results from acupressure and reflexology (''touch therapies'', 2 RCTs) which are less heterogeneous and positive. Again, the limitations in study risk of bias are reflected in the strength of evidence conclusion and not part of the judgment of whether interventions are effective. 3. We included the study by Mosher et al. as its own category because it included mindfulness (which we classified as an integrative medicine intervention in our classification of interventions), so overall, the study fit as a behavioral/ psychoeducational and an integrative medicine intervention. 4. After careful consideration, we have now included the Bruera study. Given that this was an open-label study, we disagree that it clearly demonstrates efficacy of morphine. The Mazzocato study did not meet the inclusion criteria but is noted in the discussion; as noted below given the small sample size, it would not have changed the conclusions, and there are concerns about this study as well. We have also added to the discussion issues about these older studies conducted in a time when there were many fewer treatments available for these patients. 5. We agree that there were limited studies comparing non-pharmacologic and pharmacologic interventions and

Commentator & Affiliation	Section	Comment	Response
		5. For KQ 3 (multimodel intervention), only one study was included (Minchom) examining morphine and/or acupuncture – I am not sure this is really a great study for this category (more for acupuncuture). There have been several other studies examining multimodal interventions more comprehensively but they were not included because they did not meet the strict inclusion criteria. 6. Ultimately, I am not sure how meaningful the analyses on the many other outcomes were (e.g. respiratory rate, heart rate, blood pressure, anxiety, HRQOL). The number of studies were already very limited, the sample sizes were small, not all reported these outcomes, and the study design varied a lot. I would be very cautious interpreting these exploratory findings.	that there were methodologic concerns for the Minchom study. We were able to include only the studies that met our inclusion criteria; the reviewer did not note any specific studies here for us to consider. We have now included one more study (Gottlieb et al) for Key Question 3. 6. We agree that some of these secondary outcomes are less important; these were requested by ASCO/PCORI and are often considered in clinical practice. HRQOL is generally considered an important outcome, especially as treatments for dyspnea can have significant harms and burdens. These were not considered critical outcomes and were infrequently reported, and we did not grade or emphasize these.

Commentator & Affiliation	Section	Comment	Response
Reviewer #2 (TEP)	Discussion/ Conclusion	1. The discussion included some important points highlighted above. However, I think it is critical to acknowledge where evidence is inadequate and acknowledge it as such instead of concluding that an intervention is not effective, particularly since so few effective interventions are available. It is important to recognize the limitations of many included studies and how they may limit interpretation. Many of the trials were of older design – may not specifically include patients with dyspnea, dyspnea was not the primary outcome, and/or the intervention may not be targeting dyspnea. Many of the studies were small, pilot trials and designed to estimate the within-group effect instead of between group effect. 2. Also, it is important to state that non-pharmacologic studies had open design while drug studies more often used a blinded placebo design. The risk of bias is much higher. 3. Applicability. The investigators stated that the findings may be applicable to patients with COPD; at the same time, they excluded many COPD studies. 4. Future research is inadequately developed. It is only a small paragraph here but this needs to be emphasized a lot more.	1. We agree and have expanded the limitations section of the report. We have added the concerns of the older studies (especially Bruera and Mazzocato). We have added the issues of pilot trials and study targets. 2. We have added the limitations of non-blinded (open label) design in most non-pharmacologic studies and that most pharmacologic studies were blinded, in the discussion. 3. We have clarified in the discussion that this was comorbid COPD, not patients with COPD without cancer. 4. Thank you. We have expanded the future research section, including content based on the above comments.
Reviewer #2 (TEP)	Clarity and Usability	Difficult to understand how the authors interpreted the existing evidence and how the criteria for "effective", "inconclusive" and "ineffective".	We graded the evidence as recommended by AHRQ's EPC Methods Guide for Effectiveness and Comparative Effectiveness Reviews. We applied evidence grades to the bodies of evidence for each key outcome. The overall evidence grade was assessed based on the ratings for the following domains: study limitations, directness, consistency, precision, and reporting bias. We have added more details to the report.[We added more details to the grading section [Methods appendix A –"Grading the Strength of the Body of Evidence"]

Commentator & Affiliation	Section	Comment	Response
Reviewer #2 (TEP)	Minor issues	Table 5. Kako. The word “Placebo” should be replaced. Table 15. Please report the number of patients in addition to %.	We have changed ‘’placebo’’ to ‘’sham control.’’ We have added the number of patients.
Reviewer #3	General Comments	This is an important subpopulation of seriously ill patients to consider and a very troubling symptom that patients with cancer endure. Key questions are appropriate. I worry about including 'combination' interventions as this makes it very challenging to know which component was effective. I could see including combination intervention studies if controlled by changing one aspect. In this case, KQ #3 would be eliminated since KQ #1 and KQ #2 would be able to isolate components that improve dyspnea. An example is on pg 12, row 2 of Table 3 and last column - 'multicomponent combined behavioral/psychoeducational, activity/rehabilitation and complementary and alternative medicine interventions were more effective at improving anxiety compared to usual care'.	Thank you. To clarify, if a study included interventions that were all non-pharmacologic but covered more than one intervention type (e.g., respiratory training, relaxation, and exercise), it was still classified as KQ 1. This would make it a multicomponent non-pharmacologic study. We agree that it is impossible to identify which intervention ‘’worked’’. KQ 3 refers to studies that compared pharmacologic versus non-pharmacologic interventions or a combination of both of these, which we termed “multimodal”. In an updated search, the number of studies for KQ 3 were two. We have worked to clarify this in several places (note that the request for KQ 3 was made by ASCO/PCORI/ AHRQ).
Reviewer #3	Introduction	Reference for sentence, "Objective findings (such as oxygen saturation or respiratory rate) are frequently monitored in clinical practice, but often do not correlate with symptoms." As a clinician this is what we see at the bedside, but I think this assertion is important enough to warrant re-enforcing with a reference.	We have added a reference to reinforce the point. Hui D, et al. J Palliat Med. 2013 Mar;16(3):274-80 https://www.ncbi.nlm.nih.gov/pubmed/23398052

Reviewer #3	Methods	Inclusion/exclusion: 1. Given the sparse evidence in this subpopulation with dyspnea, I am concerned about how restrictive these criteria are. With subjective symptoms where one patient's '7/10' is another patient's '3/10' in terms of dyspnea severity, it is important to consider pre-post methodology that capture the relative change (using the patient as their own control). I worry the included articles represent a small subset of data that can inform the authors' questions. As an example, on page 17 there are a number of instances where the authors comment that both arms of a study (ie. compressed air vs oxygen) improved dyspnea pre-post but there was no between group differences. Same on page 40 with opioids, but these studies are not being utilized in good faith to assess impact of opioids on dyspnea. Unless using pre-post evaluation as a valid measure, we are left concluding that either both work or don't work but do either equivalently. 2. Also, why cut studies off at a size of 10 subjects? This seems small and arbitrary - Mazzocato C et al, Ann Oncol, 1999 could be included as an example. I am not a statistician and can't comment on the appropriateness of the approach. Table 1 is a very clear summary of the inclusion/exclusion which is logical and explicit. **Secondary outcomes:**	1. Thank you for this comment. The protocol was reviewed in detail by ASCO, PCORI and the technical expert panel. We did find a wide range of literature, and in symptom management, uncontrolled studies are generally not considered adequate for informing practice given bias, placebo effects and patients often reporting lower symptom burden over time. We therefore report between group differences as the main finding. We have noted the importance of placebo effects in this literature in the discussion. We did include a number of crossover studies where patients served as their own control. 2. An exclusion of 10 participants for the protocol was decided based on input from the technical expert panel, as there are numerous very small studies with only a few patients in this field due to challenges with recruitment. As we have reported in the limitations, outcome reporting across even large, well-done studies was heterogeneous and breathlessness is a complex symptom ideally assessed by a multi-dimensional comprehensive scale. We felt that studies with <10 participants per arm were generally older with incomplete/ poor reporting of data and unidimensional dyspnea assessment, and they were at significant risk of bias (especially due to non-blinding in non-pharmacologic interventions). We did not believe that including these studies would meaningfully increase power. In fact, we believe including these studies could 'dilute' meaningful findings. Thank you. We agree and have not drawn conclusions about effectiveness for these secondary outcomes, just on the key outcomes (dyspnea, anxiety, exercise capacity (renamed from functional capacity based on comments from the panel) and HRQOL).

Commentator & Affiliation	Section	Comment	Response
		This manuscript is looking at dyspnea in cancer patients. I understand secondary outcomes, but I would argue the only clinically important ones are functional capacity, RR, and soluble blood gas (O2/CO2) as these are signs of either effectiveness or potential harm. I can see reporting on anxiety since one can have dyspnea unchanged but be less anxious about it and consider that a success. In addition, the article reports on oxygen saturation, but I don't see any reporting on carbon dioxide saturation - the subtitle "Oxygen or Carbon Dioxide/Bicarbonate Levels (Oxygen Saturation)" is not accurate since oxygen saturation does not give any information about CO2/HCO3 soluble blood levels. Transparency about how Conclusions from articles is drawn: Example - page 27, top of the page: no studies showed convincing clinically meaningful benefit, yet conclusion was positive (impact shown). If this is part of supplemental materials, then dismiss this comment. Otherwise, I would think having the 'rules' or procedure used to decide: positive benefit, no benefit, or inconclusive would help the reader that takes into account quality of studies, risk of bias, determination of clinically meaningful result, # studies/patients needed to feel confidence in conclusion.	Some studies (e.g., Nava et al) did report mm Hg of oxygen/ carbon-dioxide, apart from oxygen saturation. A priori, we did not know how many studies would report saturation vs mm Hg, and used a composite descriptive term to describe ‘’oxygen/ carbon dioxide levels.’’ Thank you, we have worked to clarify the methodology for making conclusions – for this specific example, clinical meaningfulness was difficult to determine given how the studies’ outcomes were reported; consistency and precision across studies led us to conclude effectiveness, however the uncertainty of this conclusion is reflected in the low strength of evidence. We have clarified that we followed the EPC methodology to conduct the review and drew conclusions, and we clarified this in some places in the methods (also in Methods appendix A –“Grading the Strength of the Body of Evidence”).

Reviewer #3	Results	1. In summary tables, would be good to have references so readers can know which articles are being summarized. 2. In Table 3, in the first row under 'Key findings' there is a p value of 0.76 which the text indicates is statistically significant. This is repeated throughout (pg 17, 18). I may not be understanding the statistics, but readers may think this represents a non-statistically significant result. Please explain. 3. Page 10, first row of Table 3, missing 'improvement' between 'significant ... between'. In this same row, be more consistent in use of the 'sham' language or the 'placebo' language. This row uses both which may lead to confusion in readers. 4. Page 10, row 3 of Table 3, 'Activity/rehabilitation interventions vs activity/rehabilitation interventions or usual care' very confusing as to what is being compared? Each arm needs to have a distinct label instead of the same label. 5. Page 12, use '1' or 'one' consistently - authors alternate in use. 6. Fan/cooling studies - missed Puspawati NLPD et al, Asia Pac J Oncol Nurs, 2017 (RCT, crossover design). 7. Page 15, Table 5/row 4/column 2, remove '(likely inpatient palliative care unit)' unless this is explicitly stated in original article. 8. Page 17, may want to split studies up by hypoxic and non-hypoxic patients since this seems to be an important	1. We have added these references. 2. The p value here referred to the heterogeneity, not of the meta-analysis itself. We have deleted the p values for heterogeneity. 3. We have made these changes. 4. We have clarified that one study compared two different types of activity/rehabilitation interventions. 5. We have made this change. 6. We excluded this article (Puspawati et al) since the article did not specify advanced cancer – we reviewed again to be sure. 7. We have made this change. 8. We have now presented data separately for hypoxemic patients when available; this does not change the conclusions. 9. We have removed these p values for heterogeneity as they were confusing. 10. Thank you. The studies did not explicitly present these very important confounding factors. This is

		factor in results. Not sure these should be clumped together for a meta-analysis given they are very different patient populations (and mechanisms of dyspnea). 9. Page 19, Heart Rate, text says outcome is statistically significant but p value appears to be 0.335 which is not traditionally viewed as significant. Please explain. 10. Table 6 or text relating to these studies: include potential confounding factors measures (such as pharmacologic meds used, procedures, ect). Maybe this is part of the rating of the study quality in which case please dismiss this comment. 11. Table 6, last row, 3rd column: what did the nurse do with the information or report on how often the plan changed and in what way? Was it the phone calls alone or the increased surveillance and faster change in plan that impacted outcome? 12. Page 24, HRQoL, first paragraph: sentence 'The trial found no statistically significant difference in dyspnea between groups even after crossover...' may be a misplaced sentence given this section is on HRQoL. 13. Page 27, 'Functional Status': 'reflexology' vs control - what is the control (sham reflexology or usual care)? 14. Page 28, first paragraph: acupuncture was not part of either of the references included in this section yet conclusion is that acupuncture showed improvement in HRQoL.	absolutely a reason also to downgrade the study quality which can be considered as "other" in the risk of bias assessment. We have noted this in the future research section as an important point for future studies. 11. We have clarified the details of the nursing intervention. The study did not report which aspect of nursing intervention was most impactful but both surveillance and faster in-person evaluation made a difference. 12. Thank you. We have fixed this. 13. We have clarified that the control is usual care. 14. We agree. As also suggested by our integrative medicine expert, we have removed acupuncture. 15. Mazzocato was excluded due to including < 10 patients (we have noted this in the limitations). The Pinna study was already included. After careful consideration, Bruera and Simon are included now as they did enroll 10 patients initially (although the study had attrition) 16. If we considered every type of administration and population separately, we would be very limited in the conclusions that could be drawn. For opioids vs placebo, this would not change the results. We only identified 1 study of nebulized opioids and this is already reported separately. We have noted the heterogeneity among routes of administration in the limitations/ future research section. 17. Tachypnea or change in respiratory rate is not the reason for these meds, nor is it the only signal of dyspnea. Someone can be dyspneic without being

		15. Page 33: consider allowing studies with 9 patients included - Mazzacato 1999, Bruera 1993 Ann Oncol, Simon ST 2016 JPSM (started with 10 pts but analyzed 6), Pinna MA 2015 Am J Hosp Palliat Care. 16. Page 37: Opioids vs placebo should be separated by route of administration - oral, IV, nebulized, other. 17. Page 45: given the lack of RR change with opioid dosing, this is proof the opioid was not adequately dosed (RR decreases as the CNS dyspnea signal is blunted by the opioid) 18. Table 13 seems repetitive and not necessary. Authors should present this material either in the text or as Table 13, but not both. 19. Page 53: CNS symptoms CI crosses 1.0 so this should not be a significant result, correct? 20. Page 55: clarify how drowsiness changes with corticosteroids (increases or decreases). 21. Page 56: odd to focus on diarrhea in pts getting opioids - this should be constipation which is the most common adverse effect in general with opioids.	tachypneic. Nor does someone have to stop being tachypneic (or have reduced RR) to experience relief of dyspnea. This is covered in our introduction: "Objective findings (such as oxygen saturation or respiratory rate) are frequently monitored in clinical practice, but often do not correlate with symptoms", and we have added a reference to substantiate this. 18. We have considered this comment; this was similar to our approach to Tables 11 and 12 and we have kept Table 13. 19. Thank you, we have made this correction. 20.We have clarified that patients on steroids were less drowsy. 21. Study reports were limited, particularly of adverse events, and many did not report concurrent therapies, supportive measures, or active therapies that could also be contributing to the reported adverse events that were possibly attributed to the opioids.

Commentator & Affiliation	Section	Comment	Response
Reviewer #3	Discussion/ Conclusion	Page 62: Applicability - there is a mention of comorbid COPD but I did not see that as part of the inclusion or secondary analysis of the articles included. Page 63: If changes are not planned to including studies with pre-post assessments, then I would strongly recommend a comment that included studies that assessed pre-post dyspnea suggest benefit of these agents/interventions with a caveat that in the few placebo controlled trials it was not possible to confirm these benefits are not just placebo effect. This limitation and/or conclusion is critical particularly for opioids and dyspnea since this is the standard of therapy currently and there is a reasonable evidence base for patients facing the end of life (but < 50% have cancer) that these are helpful agents. Authors could discuss why they believe their outcomes are so different then non-cancer dyspnea. Also, the most commonly used agent (morphine) is not even included in reviewed studies - this is important to list as a major limitation in the literature and therefore this manuscript's conclusions.	We have clarified and added to the future research section as well – given limitations in reporting in the studies, we were unable to analyze the impact of comorbid COPD separately. We have added in the points that placebo effects were strong in many of these studies. We have also expanded on the section on non-cancer dyspnea and added in the new, large, well-conducted studies from David Currow's group showing no effectiveness of opioids which concur with our findings (given the limitations of these studies). Other clinical practice guidelines also note the major limitations of opioids and that there are numerous types of interventions that may be considered – opioids are just one of many potential interventions; we have clarified this in the discussion. With inclusion of the Bruera study, morphine is now included in the placebo section. Opioids are similar enough pharmacologically that we have combined the different types of opioids together, as is generally done in pain. Morphine was included in numerous comparisons between different pharmacologic agents: SC vs SL morphine, SC vs nebulized morphine, oral morphine vs midazolam, SC morphine vs midazolam, and morphine vs methylprednisolone vs aminophylline.
Reviewer #3	Clarity and Usability	Categories particularly for non-pharmacological interventions were very hard to understand	We have clarified this further in the report, thank you.

Reviewer #4 (TEP)	General Comments	I believe the report is very clinically meaningful. With regards to the target population, I think we need to be clear about the term "advanced." There has been a shift away from using the term "advanced" to "incurable" given staging depends significantly based on AJCC staging criteria used. If "advanced" was the search term used, then I agree with its use over "incurable." I think that the questions are clear as stated. However, I would re-consider the order of the questions as most of the readers reviewing these guidelines will be prescribing oncologists rather than non-medical clinicians involved in non-pharmacologic approaches. I would recommend changing the order of the questions to the following: KQ2, then KQ1, KQ3, KQ4. This order also reflects the availability of these interventions across medical centers. In other words, opioids and anxiolytics are more available across sites than are multicomponent behavioral and nonpharmacologic interventions. I think that we also need to clearly state that we do not know what is the most appropriate endpoint for this patient population,. I would make sure that we are consistent in reporting data in a specific order. For example, in the abstract, data is presented as non-pharmacologic, multicomponent, and then pharmacologic. This does not reflect the order of the key questions (i.e., non-pharmacologic, pharmacologic, and then multi). An established order of data should be consistent throughout the entire manuscript to organize the reader. On page 8 under dyspnea, the multicomponent interventions are described as having low evidence. Yet, on page ES-3 under KQ3, we state that "The evidence was insufficient to draw conclusions." I am confused. It seems like this needs to be clarified throughout the report. I think we need to be more transparent regarding definitions used. I think this should be an added table to the introduction and should include definitions of	Thank you We appreciate the challenges of this definition: this was discussed in detail in consultation with ASCO and this term was used in part to be consistent with the recently released anorexia/cachexia guideline, and in part because this was generally what was used in the literature. We appreciate this comment; both NCCN and ESMO guidelines list nonpharmacologic first, so this is consistent with their use. We respectfully disagree and in our clinical practice and geographic area, nonpharmacologic options are widely available and are always used in conjunction with our first choice whenever possible. We have added to future research that more research on best endpoints is needed We have reviewed and reconciled the order of the data throughout the document, and clarified (multicomponent interventions include multiple non-pharmacologic components) For multicomponent – as above, we have worked to clarify that multicomponent is for multiple non-pharmacologic approaches (KQ1); for pharmacologic and non-pharmacologic combined, this was termed as “multimodal” by ASCO (KQ3) The definitions are in the methods appendix. We have ensured this is called out and have expanded the definitions section. We have clarified clinically meaningful for breathlessness (the key outcome of interest for ASCO) in the methods

		terms used such as the following: advanced cancer, dyspnea, dyspnea on exertion, short-term, low-dose opioids, multicomponent, usual care. Also, for readers not familiar with statistical differences, should we be clear about what a clinically meaningful difference is for each outcome? A major limitation of this met-analysis is the lack of information regarding baseline characteristics of the study population including details regarding severity of COPD, type of chemotherapy used, age, performance status, and opioid use. I recognize that it is impossible to include this level of detail in this type of study, but I think we need to be more transparent about our inability to control for baseline characteristics and how this is a limitation. The authors state that a limitation of this study is the "short-term" data of hours to days. I would argue that this is actually a strength of the study. Ethically, we cannot allow patients to remain breathless for long periods of time. Interventions must work quickly and effectively. Hence, a time period of hours to days is the most clinically relevant time period, especially in incurable cancer patients with limited prognoses. I would suggest reframing this "limitation" to a "clinically appropriate time frame for the symptom evaluated." Minor suggestions 1. confirm all references to "steroids" are changed to "corticosteroids." 2. Page 7 repeated twice 3. Tables 3,4 - can we include the endpoints used for the key findings? 4. Tables 5, 6, 7, 8 - I would suggest making the first column author, year, and n=X. For example, Wong, 2017 (n=30). The numbers are in the second column, but this makes it a bit easier to see this important data. 5. Table 5 - again, can we include the endpoints used here? We include this info in Figure 2, but would be nice to have it in the tables as well.	and ensured the additional details in the appendix are called out, and that clinically meaningful is noted throughout the document. We have added these limitations to the future research section – that this information should be consistently reported in future studies. We respectfully disagree that short-term outcomes are not a limitation, as many patients have breathlessness for more than just a few hours or days. The population of interest is advanced cancer and these patients are often now living for many years. We have added in the new studies of David Currow on longer-term chronic breathlessness management and clarified acute, exertional and chronic breathlessness in KQ 2. Minor suggestions: Done. Checked. Respectfully, we considered this, but since almost every study had a different endpoint, we did not include them here. We thought it would make the tables too complicated (details are all included in the appendix). We have revised the tables as suggested. Respectfully, since almost every study had a different endpoint, we have included it in the text and figures (and appendix) but not these summary tables.

Commentator & Affiliation	Section	Comment	Response
Reviewer #4 (TEP)	Introduction	Given the varied experience of dyspnea and the multiple endpoints used across studies, I think that we need to be more explicit about the definition of dyspnea and the endpoints used. Ideally, this would be summarized in a table.	We have added the definition of dyspnea from the ATS as suggested by another reviewer. We have added the endpoints table in Appendix C.
Reviewer #4 (TEP)	Methods	Yes, robust.	Thank you
Reviewer #4 (TEP)	Results	I think the level of detail of the results is appropriate. However, I found myself quite confused looking at each of the tables and outcomes for each endpoint. I think that we should add a table with endpoints (i.e., patient-reported dyspnea, DOE, functional outcomes, etc) as the first column with interventions in second column followed by level of evidence in the third. I think this should be the first table to summarize things based on the endpoint rather than intervention. In general, I think organizing the data based on type of intervention (non-pharm, pharm, multi) with a detailed explanation on varied endpoints is confusing. As a clinician, I would find a data presentation based on endpoints much more accessible. However, I think the current presentation reflects how the key questions were formulated. Methodologically, I understand why the data is presented in the current format, but I found it difficult to digest as a clinician.	We have added this table (organized by the key outcomes) to Appendix C (as noted below as well).

Commentator & Affiliation	Section	Comment	Response
Reviewer #4 (TEP)	Discussion/ Conclusion	For the discussion, I think it may be helpful to reference the table I recommended based on symptom (rather than intervention). As a clinician, I am getting confused when we discuss the type of intervention (non-pharm, pharm, multi) with all of the endpoints. In contrast, if we presented the findings based on endpoint (dyspnea, DOE, HRQOL, etc), I think it would be much easier to synthesize. A limitation of the discussion regarding side effects used with opioids, is that we did not assess if studies effectively prophylaxed for expected side effects of opioids. For example, standard of care would be to include a stimulant laxative when starting any dose of opioid to avoid constipation. Hard to make an conclusion regarding attribution of side effects if we do not know if the patients received appropriate medications to avoid these anticipated side effects. I think one opportunity for the future research section is for us to clearly state that a clear definition and endpoint needs to be clarified to improve the methodologic evaluation of dyspnea in patients with incurable cancer.	We have added this table to Appendix C. We agree, this information was often incompletely reported. We have added this point on the lack of reporting on other pharmacologic agents to the discussion – although constipation can be managed but not avoided and requiring treatment of a side effect with another medication can be problematic, and the side effect of constipation can be incredibly distressing. Regardless, it was difficult to conclude much about side effects given reporting issues. We have added this to the future research section.
Reviewer #5	General Comments	This systematic review/meta analysis was conducted to provide evidence to guide the development of clinical practice guidelines for ASCO to inform oncologists and oncology care teams on dyspnea management in advanced cancer. The report overall is superbly written, and have potential to meaningfully guide clinical care, despite the weaknesses identified by the review. The four key questions are appropriate and clearly stated, and encompassing both pharmacologic and non-pharmacologic interventions.	Thank you
Reviewer #5	**Introduction**	Overall, the introduction is clear and concise, and lays out the significance of the issue, and the task commissioned to the core review team.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Reviewer #5	**Methods**	Overall, methods are very clearly provided, with supplemental information included. Inclusion and exclusion criteria are justified, with clear search strategies and assessment of strength of the body of evidence.	Thank you.
Reviewer #5	**Results**	The results section is clearly presented and organized by the four key questions, with corresponding tables that summarize the findings. The tables are superb; particularly with the use of graphics to underscore the findings.	Thank you.
Reviewer #5	**Discussion/ Conclusion**	I do have several suggestions for this section. First, the implications of major findings are clearly stated, and limitations and strengths appropriately presented. The authors appropriately stated that the current body of evidence is limited by several factors, including methodologic weaknesses. On the statement for inclusion of other related outcomes, such as HRQOL, anxiety: does the authors have some recommendations on the type of measures that should be used? And for dyspnea assessment, are there other measures beyond visual analogue scale that can be used? For the future research section: given that the review found that some non-pharmacologic strategies may be more efficacious, what are the cost-related implications to clinical practice of integrating these strategies? If the goal is to encourage institutions to consider non-pharm management of dyspnea, what are some recommendations on how to implement these in real world settings? Finally, can the authors expand on the need to study informal caregiving and how caregiver's perspective may influence dyspnea management?	Thank you In the future research section, we have expanded on the types of measures and more comprehensive dyspnea measures, from Richard Mularski's review and expert consensus document on this literature. We have expanded on how non-pharmacologic options may be available in various settings. We have added this to the discussion as a very important aspect of dyspnea management.
Reviewer #6 (TEP)	**General Comments**	The report is well-written for a clinical audience with explicit key questions and responses. The PRISMA guidelines were followed. Excellent use of graphics to display results.	Thank you

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (TEP)	**Introduction**	Clear and well-referenced. Using the drug class opioids here and throughout the narrative implies that all drugs in the class have been studied when in fact only morphine and some formulations of fentanyl have an evidence base.	Thank you. Hydromorphone was also studied and included; opioids are generally considered as pharmacologically relatively equivalent. Also, one study did not list the types of opioids used and instead reported the difference between “high dose and low dose opioids”. Given this, we decided to report the results by the drug class.
Reviewer #6 (TEP)	**Methods**	A large body of dyspnea evidence for patients with COPD were excluded. The authors did provide a clinical justification in the discussion, however, many lung cancer patients also have COPD and the exclusion of that body of research leaves very little to report.	Our charge from ASCO was to address cancer patients; the COPD literature has been addressed in other recent systematic reviews, but we definitely agree that comorbid COPD is a very important issue – we have added the results from the Cochrane review on COPD specifically and David Currow’s new papers (published since the draft report was written) to the discussion.
Reviewer #6 (TEP)	**Results**	The results were clear with extensive detail in the appendices. Clear graphics. Dose and duration of relief is an important finding that was not reported in the main document. Acupressure requires special training and while effective may not be universally available in the US. Studies with mixed samples of cancer and COPD should have been included.	Thank you We have clarified. We have noted this in the discussion. Our charge from ASCO was to focus on cancer patients. Our protocol was to include studies if more than half were cancer patients or if cancer outcomes were reported separately.
Reviewer #6 (TEP)	**Discussion/ Conclusion**	The implications about the evidence for morphine were understated. A clinical toolkit for dyspnea treatment in advanced cancer has little in it if clinicians fear, during an opioid overuse climate, to use the medication that has the "stamp of approval" from clinician's anecdotal experience. The future research section could have more detail with suggested research questions, methods, and priority areas.	We have reworded the opioid statements as per other comments, to be clear that the conclusions about opioids are within the limits of the included studies. We have expanded the future research section as per your and other comments.

Commentator & Affiliation	Section	Comment	Response
Reviewer #7	**General Comments**	The report is meaningful in populations of patients suffering from dyspnea from lung cancer, as most of the studies included here were lung cancer specific. Key points are appropriate and the audience is well defined. However, treatment of dyspnea arising from other causes that might arise in the setting of advanced cancer (severe anemia, deconditioned state, etc) is not well described.	We have reorganized he introduction to be clear that these were out of the scope of our review.
Reviewer #7	**Introduction**	Well-written. No comments.	Thank you
Reviewer #7	**Methods**	Table of inclusion/exclusion criteria is present, easy to follow, and reasonable. Search strategies are defined though these are placed in the appendix.	Thank you
Reviewer #7	**Results**	The amount of detail in Results is appropriate. Characteristics of studies are well described and key messages are explicit and applicable. Figures are appropriate.	Thank you
Reviewer #7	**Discussion/ Conclusion**	Implications of major findings are clearly stated. Future research section is very short and written in broad terms, is lacking in detail and seems not to be easily translated into new research as is written.	Thank you
Reviewer #8 (TEP)	**General Comments**	Overall this is very well done and a necessary and applicable review. The target population and audience are defined. I would encourage the authors to include a "definitions" section in the report or supplement to define some relevant terms and provide clarity on types of dyspnea studied, hypoxemia definitions in the studies, etc. I referenced specific comments on these below. The report was very clear, well organized, and the tables and forest plots balanced the information with some helpful visual cues to reinforce concepts and deepen understanding.	Thank you. We have ensured the call out to the definitions section is clear (this is in the methods appendix) and have included these definitions here. We have also clarified the dyspnea types in the introduction and in KQ 2 in particular.

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 (TEP)	**Introduction**	Page 13, line 32: “cooling through fan therapy…” – Are you suggesting that all of those treatment modalities are helpful because of theories involving stimulation of TRPM8 channels on trigeminal neurons and vagal afferents which correlate to cold sensitivity? My understanding is that fan therapy or air movement therapy is thought to be effective due to the air movement aspect activating trigeminal nerve facial receptors which tricks the brain into believing ventilatory flow is higher than it is. This may be in addition to the theory mentioned above with TRPM8 channels. There has been data showing that the fan/air flow is not effective if used on other parts of the body (so the cooling piece alone in other areas isn’t helpful). I worry that the language used above is misleading as to the theories of mechanism of action. If there is more definitive data as to the mechanisms of action of the respiratory interventions in that sentence, please disregard.	We did not mean to suggest the pathophysiologic basis of the effectiveness of these interventions when we wrote, ‘’cooling through fan therapy.’’ We agree the language is misleading and that the mechanism may be air movement. We have removed the words ‘’cooling through’’, and just left ‘’fan therapy,’’ and renamed “airflow/cooling” as “airflow”.

Commentator & Affiliation	Section	Comment	Response
Reviewer #8 (TEP)	**Methods**	a. Regarding exclusion criteria for not reporting a comparison group, my understanding is that studies were only included if a concurrent comparator group was present. What is the rationale of excluding studies that included the patient as their own control (if any existed)? b. Regarding outcomes, it is unclear as to whether studies were included if they evaluated all the patient/caregiver reported or observational outcomes in addition to clinical or utilization outcomes? Or were they included if they reported at least 1 patient/caregiver/observational outcome in addition to clinical outcomes? c. Clinically Important Difference definition – I understand that this metric is not clearly defined. What about the data that suggests that the placebo effect can improve patient-reported symptoms of an intervention by up to 30%?	a. We included studies where patients acted as their own controls (i.e., - crossover studies). Several of the respiratory intervention studies were crossover studies, as indicated in Table 5 (example Wong, et al, Booth et al). We did not find any studies where there was no concurrent comparison group and only a single cohort of patients received an intervention, followed by a washout period, followed by the same cohort receiving another intervention. b. Studies were included if they reported patient or caregiver reported dyspnea. – we have clarified this in Table 1. They could also report other patient or caregiver outcomes such as anxiety, functional status, and HRQOL. There was no requirement for a study to report the other 3 patient or caregiver outcomes, or to report any one of other clinical or utilization health outcomes such as respiratory rate. c. We have now noted the importance of the placebo effects in these studies in the discussion.

Reviewer #8 (TEP)	**Results**	a. I feel that the way the authors presented the information in the tables of "Summary of key findings" (Tables 3, 11, etc.) is superb. They include the main points in a concise manner with some visual cues to enhance understanding and make the information more digestible quickly. I had some follow-up questions after reading some of the summaries and was able to quickly find the category of intervention in the "Description of Included Studies" Table to dive deeper. b. Please ensure consistency and clarity in description of study characteristics. For example, in Table 5 Kako, 2018 – "baseline ≥ 3/10 dyspnea on numeric rating scale" vs Bruera 2003 in same table "non-hypoxemic, with ≥ 3/10 on numeric rating scale". I am assuming the ">/= 3/10 on the numeric rating scale is referring to baseline dyspnea rating but feel this needs to be clarified as it was a bit confusing and I had to read and re-read to make sure I was understanding. There are a few of these throughout the table. I would like to clearly see it stated "baseline dyspnea (number) on (rating scale)" to enhance clarity. c. What is the general definition of "hypoxemic" that is used throughout? Or does it differ based on individual study? It is referenced a lot in the study characteristics but I was unable to find a working definition in the review itself or supplemental materials. It may be worth providing a working definition, even if it is a range based on study composite, for reader reference/clarity. i. I also feel it would be helpful to have some brief definitions as to the different types of dyspnea that are evaluated in these studies since they vary. This was not in the report or the supplemental appendix.	a. Thank you. b. We have clarified baseline dyspnea and defined hypoxemia at each point it is mentioned in tables. c. Most studies defined hypoxemia as oxygen saturation <90% while breathing room air, at rest. We have now included this in the definitions section as well. d. Thank you. e. Some studies did not require or specify a certain baseline dyspnea score. We have clarified as able.

Commentator & Affiliation	Section	Comment	Response
		d. The forest plots are nicely done, I appreciate that they are not overly condensed, small, and hard to read. e. Based on the title and how the information is presented in “Study characteristics” in Tables 6, 7, 9 and 10, it is unclear how these studies directly relate to dyspnea. The way it is presented, it seems as though these studies focused on patients with advanced cancer who may or may not have had dyspnea. Please make this clearer to help the reader understand the relevance of why they are included in the review. The only studies that mention dyspnea are Table 7, Molassiotis, 2017 “refractory dyspnea at rest or minimal exertion” and Table 10, Farquhar (year is missing here), “Lung cancer/ mesothelioma (54%), referred to breathlessness service” so the reader assumes baseline dyspnea. f. Although slightly clearer, Table 8 needs some revision as well. There are a few studies noting dyspnea and scale. For these, please denote if this is at baseline. For the rest, please include the dyspnea information.	f. We have clarified tables as in point e. above

Reviewer #8 (TEP)	**Discussion/ Conclusion**	a. Referencing Page 37 lines 39 – 44, I have some concerns with the overall take away noting that the timeframe of absorption and distribution of the opioid would impact the time to affect. For example, the opioids given transmucosal (if this was the fentanyl product Actiq®, it takes 15 minutes to administer) or subcutaneously would not likely have an effect at the 6 – 10-minute timeframe based on pharmacokinetics. Was the PK of the intervention accounted for in the studies (both for opioids and anxiolytics)? Was it appropriate? I feel this should be denoted in the discussion as many people will have these same questions, especially since opioids have traditionally been a standard treatment selection in dyspnea in palliative care (and anxiolytics as well). This isn't currently addressed in the paragraph on pharmacologic interventions on page 60 lines 32 – 42. b. Page 62, lines 48 – 50, I worry that the way this is stated, it could be interpreted that you are referring to opioid use for pain or other comfort measures here, for which we know opioids are appropriate at end of life. Please reword to clarify this point as it pertains to opioid use for dyspnea. c. I feel that the rest of this section is nicely done. There are many highlighted areas of need for future research that would be easily translated into study design.	a. For these specific studies: we assume that the timeframe for the opioids was appropriate in these studies: #68 – buccal tablet, 6 minute walking test started 30 min after dose #82 – nasal spray, 6 minute walking test started 20 min after dose #100 – SC fentanyl, 6 minute walking test started 15 min after dose #119 – oral transmucosal, 6 minute walking test started "once fully consumed" The fentanyl for exertional dyspnea studies say the dose was given a certain number of minutes before the 6 minute walking test due to correspondence with peak. This is mainly an issue for the buccal tablet as IN and SC doses are given quickly. It is perhaps implied although not explicitly stated that the 6 minute walking test is 30 min after full ingestion of the product. Based on drug database (Lexicomp) Time to peak: Buccal tablet: 20 – 240 minutes (median: 47 minutes) Lozenge: 20 – 480 minutes (median: 20 – 40 minutes) Intranasal: median: 15 – 21 minutes SC bolus: 10 – 30 minutes (median: 15 minutes) SL tablet: 15 to 240 minutes (median: 30 – 60 minutes) b. We have clarified the conclusions on opioids throughout, based also on other reviewers' helpful comments on appropriate wording. c. We have expanded the future research section

Reviewer #8 (TEP)	**Clarity and Usability**	This is the same information as presented in the results review, but it is pertinent here as well. b. Please ensure consistency and clarity in description of study characteristics. For example, in Table 5 Kako, 2018 – "baseline ≥ 3/10 dyspnea on numeric rating scale" vs Bruera 2003 in same table "non-hypoxemic, with ≥ 3/10 on numeric rating scale". I am assuming the ">/= 3/10 on the numeric rating scale is referring to baseline dyspnea rating but feel this needs to be clarified as it was a bit confusing and I had to read and re-read to make sure I was understanding. There are a few of these throughout the table. I would like to clearly see it stated "baseline dyspnea (number) on (rating scale)" to enhance clarity. c. What is the general definition of "hypoxemic" that is used throughout? Or does it differ based on individual study? It is referenced a lot in the study characteristics but I was unable to find a working definition in the review itself or supplemental materials. It may be worth providing a working definition, even if it is a range based on study composite, for reader reference/clarity. d. I also feel it would be helpful to have some brief definitions as to the different types of dyspnea that are evaluated in these studies since they vary. This was not in the report or the supplemental appendix. e. Based on the title and how the information is presented in "Study characteristics" in Tables 6, 7, 9 and 10, it is unclear how these studies directly relate to dyspnea. The way it is presented, it seems as though these studies focused on patients with advanced cancer who may or may not have had dyspnea. Please make this clearer to help	b. We have clarified baseline dyspnea and defined hypoxemia at each point it is mentioned in tables. c. Most studies defined hypoxemia as oxygen saturation <90% while breathing room air, at rest. We have now included this in the definitions section as well. d. Definitions of common terms used in the report are in the Appendix A (Table A-3). e. Some studies did not require or specify a certain baseline dyspnea score. We have clarified as able. f. We have clarified tables as in point e. above

Commentator & Affiliation	Section	Comment	Response
		the reader understand the relevance of why they are included in the review. The only studies that mention dyspnea are Table 7, Molassiotis, 2017 “refractory dyspnea at rest or minimal exertion” and Table 10, Farquhar (year is missing here), “Lung cancer/ mesothelioma (54%), referred to breathlessness service” so the reader assumes baseline dyspnea. f. Although slightly clearer, Table 8 needs some revision as well. There are a few studies noting dyspnea and scale. For these, please denote if this is at baseline. For the rest, please include the dyspnea information.	
Reviewer #9	**GENERAL**	This is a commissioned systematic review of some of the general nonpharmacological and pharmacological approaches to the relief of dyspnea in cancer patients developed to assist ASCO in the development of their clinical practice guidelines Overall this is a monumental and comprehensive undertaking that has highlighted the thin and very limited evidence base for many of the practices that have either been recommended or endorsed. This is an excellent work that constants the most comprehensive review of this data that I have set seen presented. I have few criticisms. I will confine my comments to 2 issues: Scope of non pharmacologic interventions and the section on opioids	Thank you

Commentator & Affiliation	Section	Comment	Response
Reviewer #9	**SCOPE**	It is important to note and to acknowledge that the scope of this review does not include the full range of pharmacological and nonpharmacological interventions in the management of dyspnea, in so far as it does not address the impact of multiple interventions that may be specific to identifiable underlying pathology is contributing to dyspnea for instance: [PLEASE SEE THE ATTACHED DOCUMENT] Consequently, in describing the scope of this systemic review it would be more accurate to describe it as a systemic review of symptomatic management.	Thank you, these were out of scope given our charge from ASCO – we have reorganized the introduction to make this point clearer to the reader.
Reviewer #9	**KQ2 -OPIOIDS**	**Completeness** [PLEASE SEE THE ATTACHED DOCUMENT] The systematic review regarding the use of opioids, and in particular systemic opioids in the relief of dyspnea in cancer patients highlights several problems characterizing this literature: Small studies and study endpoints may not be generalizable to the more global experience of breathlessness. Two well known studies (both positive) seem to be conspicuously missing from this review 1. Mazzocato C , Buclin T , Rapin CH . The effects of morphine on dyspnea and ventilatory function in elderly patients with advanced cancer: A randomized double blind controlled trial . Ann Oncol 1999 ; 10 : 1511 – 4 . 2. Bruera E , MacEachern T , Ripamonti C , Hanson J . Subcutaneous morphine for dyspnea in cancer patients . Ann Intern Med 1993 ; 119 : 906 – 7 . These missing studies may in part account in for the variance of this review with the Cochrane review 2016. Please consider incorporating these studies and recalculating benefit scores	After consideration, we have now included the Bruera study. The Mazzocato study did not meet the inclusion criteria (as only 9 patients enrolled) but we have noted it in the discussion; given these were small studies, neither changes the results meaningfully.

Commentator & Affiliation	Section	Comment	Response
Reviewer #9	**Conclusions**	In the discussion there is a discrepancy between critical the statements relating to opioid pharmacotherapy (lines 32-33 p60) " opioids were not effective for the outcomes of dyspenea or functional capacity within the limits of the identified strudies focusing on exterional dyspea". This is a balanced and qualified statement. (p61 lines 22-23) "For phamcological interventions , we did not find evidence to support the effectiveness of opioids". This very definitive assertion lacks all of the previously stated nuance. It is overly definitive, neglecting the variance in the studies (some of which are positive) and the limitations of the study design endpoints which were alluded to later and in the subsequent sections on strengths and limitations and implications. Especially at a time when globally the use of opioids has been critical in relieving distress caused by terminal dyspnea in the COVID pandemic, the weakness of the evidence base should framed in terms that are not nihistic to the point os suggesting that opioids are a futile intervention. There is an issue of balance in the report's conclusion regarding opioids that needs to refined with a greater focus on circumspection rather than nihilsm	We appreciate this comment and have changed to better fit the wording in the 1st statement as you suggest.

Commentator & Affiliation	Section	Comment	Response
Public Comments #1 [National Comprehensive Cancer Network]	**Overall**	NCCN applauds AHRQ for acknowledging the importance of evidence in determining appropriate care and treatment of cancer patients, and appreciates the thoughtful and thorough draft review. The proposed review, however, contains an inaccurate statement regarding the emphasis placed on specific NCCN Guideline recommendations. As such, NCCN would like to provide clarifying information on our guidelines development process and the evidence-base for our guideline recommendations. [PLEASE SEE THE ATTACHED PDF] NCCN suggests amending the following statement found on page 61 of the draft report: [see attached pdf]	We have amended this statement (the original statement was based on the written text portion of the guideline which is what NCCN provided in response to our initial request – which is almost totally about opioids, much of which is about non-RCT evidence for effectiveness). We would be very glad to provide any input/ additional information if NCCN uses our systematic review for the next update of their guideline this year.

Public Comments #2 Stefano Nava Alma Mater Studiorum University, Bologna	**Key Question 1**	I insert here most of my comments, since they may apply for all the section: - BPAP is NOT the usual definition of bilevel positive pressure. (BiPAP is largely used, despite it was also a brand name, so we can alternatively use bilevel ventilation - I strongly support also to insert in the non pharmacological paragraph the use of High Flow Nasal Cannula (HFNC), that is otherwise called High Flow Oxygen, that may be confused with standard oxygen with a flow > 10 L/min. Despite one short term RCT, the use of HFNC is very popular in real life and there are a couple of observation studies. This may merit a space in the Discussion - Instead of supplemental oxygen I propose to use standard supplemental oxygen - A defintion of standard supplemental oxygen vs HFNC is mandatory in my view - I was wondering if it is worth to made an analysis of the whole treatments between patients with Acute Respiratory Failure vs patients with Acute Respiratory Failure. If not we may stress in the Discussions the difference potential mechanisms of dyspnea in the acute vs chronic situation (i.e. chemoreceptors or strain receptors)	We have updated ‘’BPAP/ Bipap/ NPPV’’ to ‘’bilevel ventilation’’ throughout the report. We have clarified the wording in the portions of this review addressing this intervention. We have updated ‘’High Flow Oxygen’’ to ‘’High Flow Nasal Cannula’’ throughout the report. We have updated ‘’supplemental oxygen’’ to ‘’standard supplemental oxygen’’ throughout the report. We have included a definition of standard supplemental oxygen and High Flow Nasal Cannula (HFNC) in the definitions section. • Standard supplemental oxygen: conventional oxygen therapy delivered via nasal cannula or face masks, can achieve flow rates of up to 15 L/min. However, these flow rates may be significantly lower than patients' spontaneous inspiratory flow rates and the oxygen is diluted as it is mixed with room air. • HFNC: delivers a humidified, heated, air oxygen blend (allowing from 21% to 100% FiO2) generating up to 60 L/min flow rates through a large diameter nasal cannula We have ensured that we are clearly noting where patients had acute respiratory failure – there are very few of these studies. We appreciate this comment and have added to the discussion (applicability section) the important differences between treatment of acute episodes and chronic dyspnea, particularly for some types of interventions such as bilevel ventilation and HFNC.