Palliative and Supportive Care

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Prophylaxis and treatment of cancer-related dyspnea with pharmacologic agents: A systematic review and network meta-analysis

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Review Article

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Abstract

Introduction. Cancer-related dyspnea is a common symptom in patients with cancer. It has also been reported to be a predictor of poorer prognosis, which can then change clinical treatment and advance care planning. Currently, no definitive recommendation for pharmacologic agents for cancer-related dyspnea exists. The aim of this systematic review and network meta-analysis is to compare pharmacologic agents for the prophylaxis and treatment of cancer-related dyspnea.
Methods. A search was conducted in the databases of PubMed, Embase, and Cochrane CENTRAL through May 2021. Standardized mean differences (SMDs), as reported by studies or calculated from baseline and follow-up dyspnea scores, were amalgamated into a summary SMD and 95% confidence interval (CI) using a restricted maximum likelihood multivariate network meta-analysis.
Results. Twelve studies were included in this review; six reported on prophylaxis of exertional dyspnea, five on treatment of everyday dyspnea, and one on treatment of episodic dyspnea. Morphine sulfate was better at controlling everyday dyspnea than placebo (SMD 1.210; 95% CI: 0.415–2.005). Heterogeneity in study design and comparisons, however, led to some concerns with the underlying consistency assumption in network meta-analysis design.
Conclusion. Optimal pharmacologic interventions for cancer-related dyspnea could not be determined based on this analysis. Further trials are needed to report on the efficacy of pharmacologic interventions for the prophylaxis and treatment of cancer-related dyspnea.

Introduction

Cancer-related dyspnea is a common and distressing symptom for patients with cancer (Jones and Simone, 2014). According to a meta-analysis by Solano et al. (2006), between 10% and 70% of patients may experience dyspnea. In addition to being a distressing symptom (Tishelman et al., 2007), dyspnea is also a predictor of shortened prognosis. Clinical treatment and advance care planning may change based on both dyspnea symptomatology and prognostic information (Pinna et al., 2009; Simone and Jones, 2013).

A recent clinical practice guideline by the American Society of Clinical Oncology discusses nonpharmacologic interventions to relieve cancer-related dyspnea, including airflow interventions, supplemental oxygen, and other psychoeducational and self-management approaches (Hui et al., 2021). For patients where nonpharmacologic interventions are insufficient, pharmacologic interventions including systemic opioids, short-acting benzodiazepines, systemic corticosteroids, and bronchodilators have been recommended. However, the strength of recommendations are weak to moderate given the paucity of randomized controlled trials (RCTs) conducted to date.

In an attempt to increase statistical power, a network meta-analysis can be used to generate indirect comparisons of pharmacologic interventions to one another. Through this, further clarity might be provided regarding which pharmacologic interventions may have the most promise for future clinical trials. The aim of this study was to conduct a systematic review and network meta-analysis of RCTs to determine the optimal pharmacologic interventions for the prophylaxis and treatment of cancer-related dyspnea.

Methods

Search strategy

A search was conducted in the databases of PubMed, Embase, and Cochrane CENTRAL (Appendix 1). The databases were searched through to May 4, 2021. No language restriction was placed.

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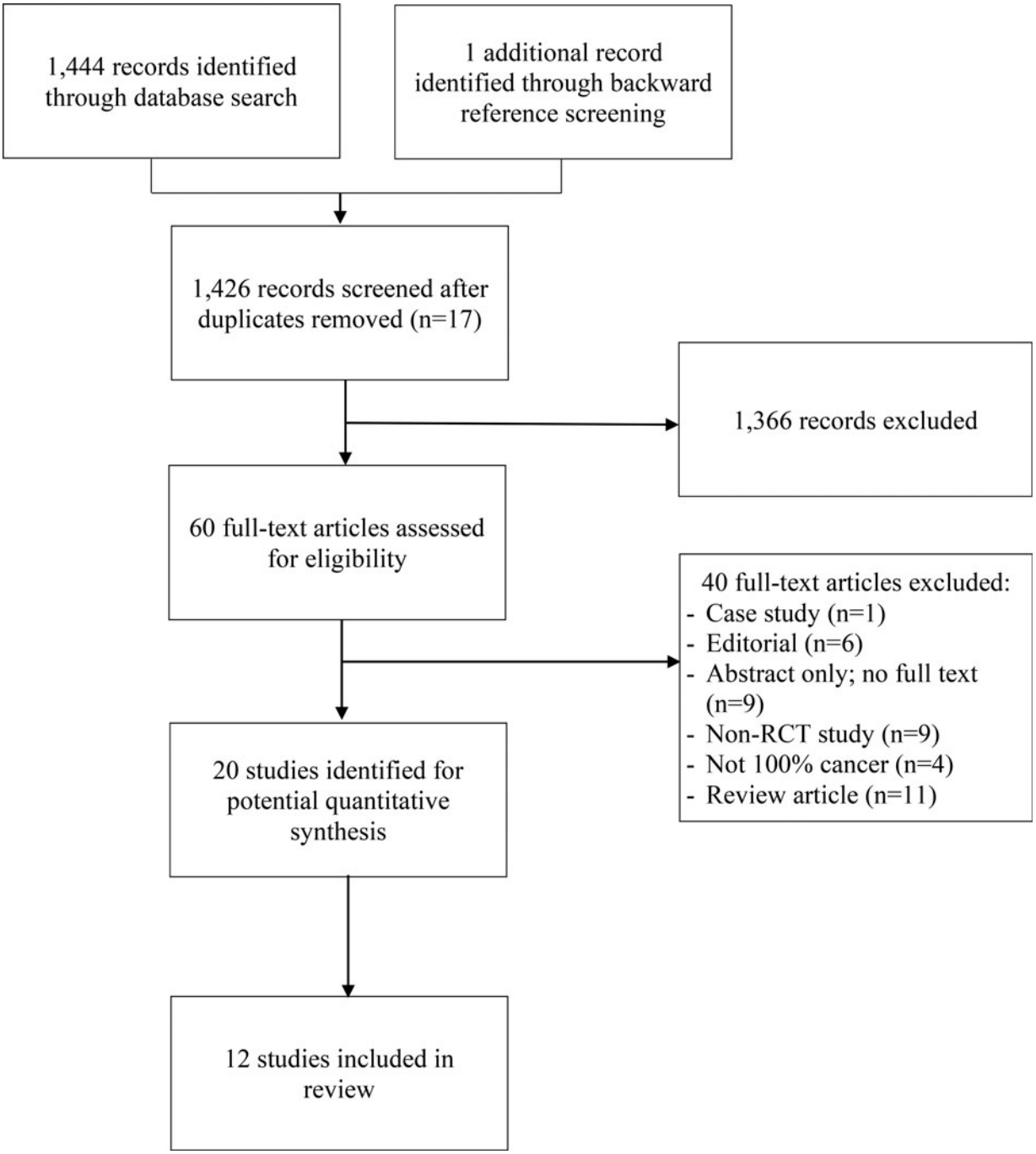

Fig. 1. PRISMA flow diagram.

Inclusion criteria

All articles from the search strategy and identified through backward reference screening underwent level 1 title and abstract screening. Articles were eligible for level 2 full-text screening if they reported on a clinical trial of pharmacologic treatments of dyspnea. Level 2 screening subsequently identified articles that were RCTs and reported exclusively on cancer patients. Eligible articles then underwent assessment for quantitative synthesis, and they were included in this review if they reported either (1) standardized mean differences (SMDs) of dyspnea symptoms from baseline to follow-up or (2) baseline and follow-up dyspnea scores. For articles where insufficient data were provided in the manuscript, corresponding authors were contacted twice, two weeks apart. In cases where no response was provided or no data were available, the study was excluded from this review.

Risk of bias assessment

Studies were assessed for risk of bias using the Cochrane Risk of Bias version 2 tool (Sterne et al., 2019). Risk of bias was presented in this study using the Risk-of-bias VISualization package (McGuinness and Higgins, 2020).

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Table 1. Study demographics

Study	Sample size	Study design	Cancer diagnosis	Mean age	% Male	Comparative treatments	Measurement tool
Bruera et al. (1993)	10	Double-blind, crossover	Terminally ill cancer	NR	NR	(1) Morphine, sulfate (2) Placebo	VAS
Charles et al. (2008)	20	Double-blind, crossover	Any cancer	69	45	(1) Hydromorphone, nebulized (2) Hydromorphone, systemic (3) Placebo	VAS
Gamborg et al. (2013)	20	Double-blind	Lung cancer	NR	10	(1) Morphine, hydrochlorate (2) Morphine, sulfate	VAS
Hui et al. (2014)	20	Double-blind	Any cancer	55	45	(1) Fentanyl, parenteral (2) Placebo	NRS
Hui et al. (2016b)	24	Double-blind	Any cancer	52	46	(1) Fentanyl, rapid onset (2) Placebo	NRS
Hui et al. (2016a)	41	Double-blind	Cancer with lung involvement	63	39	(1) Fentanyl, dexamethasone (2) Placebo	NRS
Hui et al. (2017)	20	Double-blind	Any cancer	55	40	(1) Fentanyl, rapid onset (2) Placebo	NRS
Hui et al. (2019)	30	Double-blind	Any cancer	52	33	(1) Fentanyl, rapid onset (high dose) (2) Fentanyl, rapid onset	NRS
Mazzocato et al. (1999)	7	Double-blind, crossover	Advanced cancer	73	44	(1) Morphine, sulfate (2) Placebo	VAS
Pinna et al. (2015)	13	Double-blind, crossover	Advanced cancer	65	84	(1) Fentanyl, rapid onset (2) Placebo	NRS
Simon et al. (2016)	10	Open-label, crossover	Incurable cancer	58	60	(1) Fentanyl, rapid onset (2) Morphine, hydrochlorate	VAS
Yamaguchi et al. (2018)	17	Open-label	Advanced cancer	66	59	(1) Oxycodone, oral (2) Morphine, sulfate	NRS

Legend: NR, not reported; NRS, numeric rating scale; VAS, visual analog scale.

Meta-analysis

Patient demographics and treatment characteristics were recorded for each included study. SMDs, as reported by studies or calculated from baseline and follow-up dyspnea scores, were amalgamated into a summary SMD and 95% confidence interval (CI) using a restricted maximum likelihood multivariate network meta-analysis. Meta-analyses were conducted separately for studies reporting on prophylaxis for exertional dyspnea and for studies reporting on treatment of everyday dyspnea. The selected study arms were grouped into three categories of treatments. We categorized treatments of buccal, nasal and sublingual fentanyl into rapid onset fentanyl, treatments of subcutaneous and intravenous fentanyl as parenteral fentanyl, and all treatments of morphine sulfate together. Although pharmacokinetics differed between treatments of different treatment routes, we pooled them together to increase statistical power. The underlying consistency assumption was assessed using an inconsistency model (White et al., 2012). *P*-values less than 0.05 were defined as statistically significant. All analyses were conducted using Stata version 17.0 (StataCorp, College Station, TX, USA).

Results

A total of 1,444 records were identified through our database searches; 1 additional record was identified through backward reference screening. After 17 duplicates were removed, 60 of 1,426 records underwent level 2 full-text screening. Twenty articles were identified for potential quantitative synthesis, and 12 articles (Bruera et al., 1993; Mazzocato et al., 1999; Charles et al., 2008; Gamborg et al., 2013; Hui et al., 2014, 2016a, 2016b, 2017, 2019; Pinna et al., 2015; Simon et al., 2016; Yamaguchi et al., 2018) were included in this review. Eight articles (Allard et al., 1999; Stone et al., 2002; Bruera et al., 2005; Navigante et al., 2006, 2010; Wilcock et al., 2008; Peoples et al., 2016; Aabom et al., 2020) were excluded on the basis of insufficient data for analysis (Figure 1).

Study demographics are presented in Table 1. Two studies were open-label, while all others were double-blind studies. Five studies employed a crossover design. Five studies enrolled patients with any type and stage of cancer, five others enrolled only patients with advanced or incurable cancer, and two reported only on patients with lung cancer. Over half of the articles had an overall low risk of bias (Figure 2).

Prophylaxis for exertional dyspnea

Six studies (Hui et al., 2014, 2016a, 2016b, 2017, 2019; Pinna et al., 2015) reported on the prophylaxis for exertional dyspnea. Three studies (Pinna et al., 2015; Hui et al., 2016b, 2017) compared rapid onset fentanyl relative to placebo, whereas one study each reported on parenteral fentanyl relative to placebo (Hui et al., 2014), dexamethasone relative to placebo (Hui et al.,

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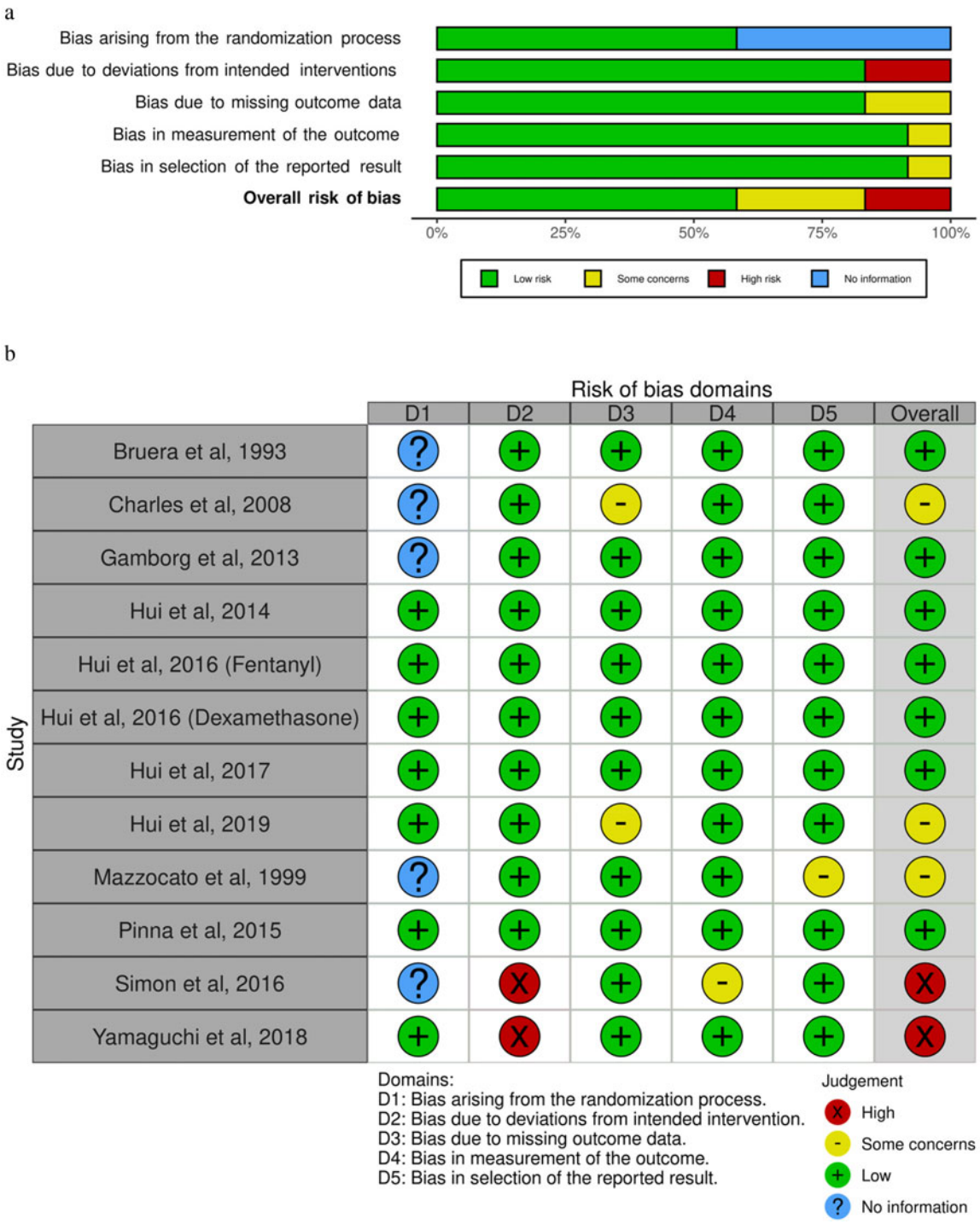

Fig. 2. Risk of bias assessment (a) summary and (b) by study.

2016a), and high-dose rapid onset fentanyl relative to rapid onset fentanyl (Hui et al., 2019) (Appendix 2a).

Rapid onset fentanyl had similar prophylactic effects on dyspnea compared with placebo (SMD 0.179; 95% CI: −0.495 to 0.853). Individual studies by Hui et al. in 2014 (Hui et al., 2014), 2016 (Hui et al., 2016a), and 2019 (Hui et al., 2019) reported no difference between parenteral fentanyl to placebo, dexamethasone to placebo, and high-dose rapid onset fentanyl compared with rapid onset fentanyl, respectively (Figure 3a).

Treatment of everyday dyspnea

Five studies (Bruera et al., 1993; Mazzocato et al., 1999; Charles et al., 2008; Gamborg et al., 2013; Yamaguchi et al., 2018) reported on the treatment of everyday dyspnea. Morphine sulfate was compared to placebo in two studies (Bruera et al., 1993; Mazzocato et al., 1999) and to morphine hydrochlorate in one study (Gamborg et al., 2013). Charles et al. (2008) conducted a three-arm studying comparing morphine sulfate to morphine

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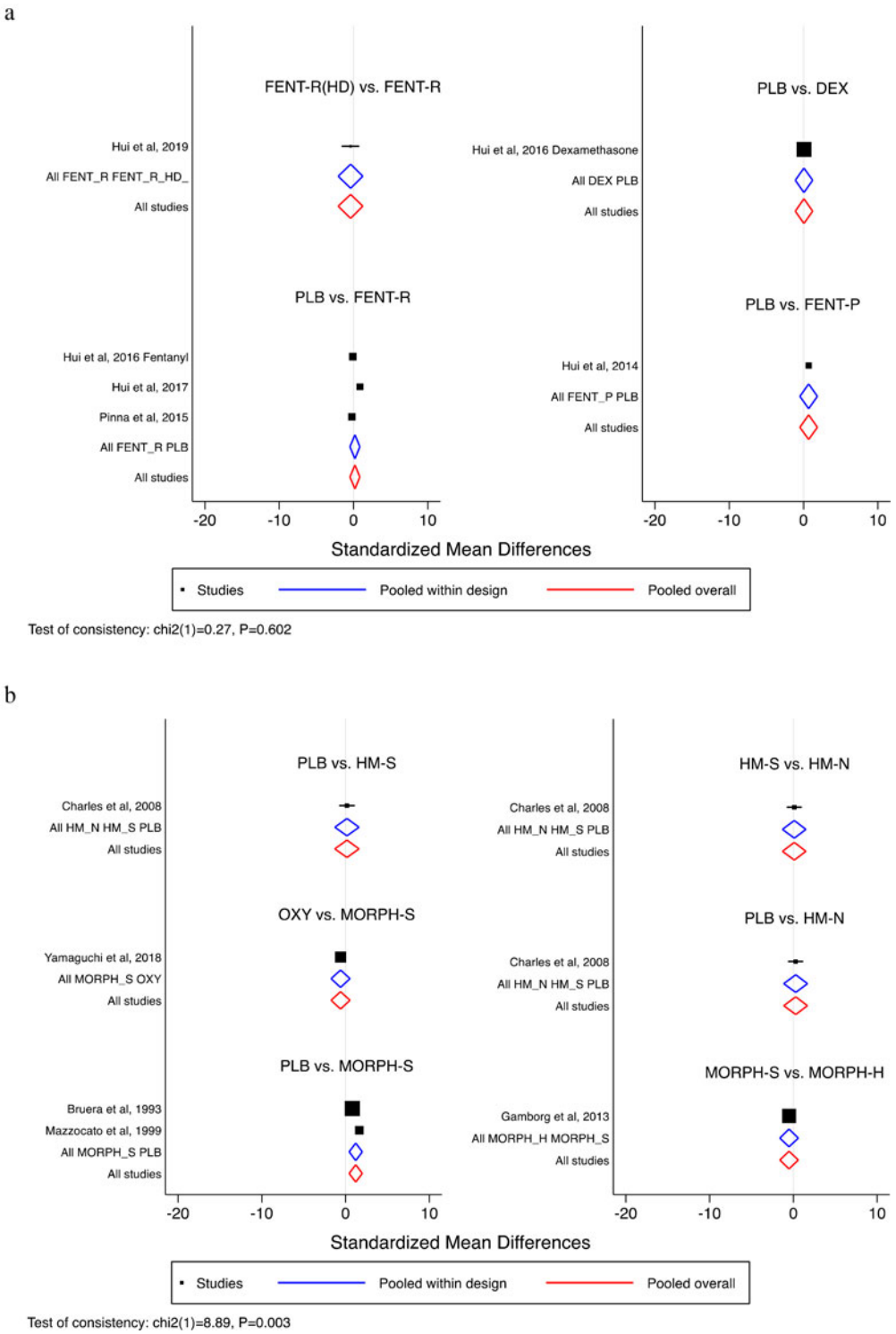

Fig. 3. Comparative efficacy of pharmacologic intervention. By study (a) prophylaxis for exertional dyspnea and (b) treatment of everyday dyspnea. Legend: DEX, dexamethasone; FENT-P, fentanyl, parenteral; FENT-R, fentanyl, rapid onset; FENT-R(HD), fentanyl, rapid onset, high dose; HM-N, hydromorphone, nebulized; HM-S, hydromorphone, systemic; MORPH-H, morphine, hydrochlorate; MORPH-S, morphine, sulfate; OXY, oxycodone, oral; PLB, placebo.

hydrochlorate to placebo. One study (Yamaguchi et al., 2018) compared morphine sulfate to oral oxycodone (Appendix 2b).

Morphine sulfate is better at controlling everyday dyspnea than placebo (SMD 1.210; 95% CI: 0.415–2.005). As reported by individual studies, no other significant pairwise comparisons were observed (Figure 3b).

Treatment of episodic dyspnea

One study by Simon et al. (2016) reported on the treatment of exertional dyspnea. No difference was reported between rapid onset fentanyl and placebo for the treatment of exertional dyspnea.

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Discussion

To our knowledge, this is the first network meta-analysis reporting on pharmacologic treatments of cancer-related dyspnea. We report on 12 studies, with a total sample size of 232 patients. Given this small sample size, and the lack of common comparisons (i.e., many pairwise comparisons are only reported in one to three studies), indirect comparisons were ill-powered or not possible. In fact, the consistency assumption is not upheld in the analysis of studies reporting on treatment of everyday dyspnea.

We report no difference between nearly all pairwise comparisons, except for morphine sulfate to placebo in the setting of treatment of everyday dyspnea. Based on the results of two studies by Bruera et al. (1993) and Mazzocato et al. (1999), morphine sulfate may be superior to placebo in the treatment of everyday dyspnea. However, caution is needed when interpreting these findings, as these two studies only had a combined sample size of 17 patients; further investigation is needed to determine if this is a true effect of superiority.

The aforementioned results, however, need to be interpreted in lieu of the strength of the literature base. Although there is a generally low risk of bias across studies, 9 of 11 pairwise comparisons reported in this meta-analysis have only one study reporting on the said comparison. As well, several notable limitations exist in the literature base — many studies are heterogeneous in design and pharmacologic agents, have a small sample size that is not powered for between-group comparison, are preliminary in nature albeit showing interesting within-group effect, were single dose and/or single-center studies, and had multiple outcomes with the risk of false positives. Given these concerns with the literature base and the limited statistical power, a conventional network meta-analysis is not appropriate at this time. We, therefore, conclude that there currently is insufficient data to recommend any one treatment rather than conclude that there is no one superior treatment. This conclusion is in line with the latest clinical guidelines by the American Society of Clinical Oncology (Hui et al., 2021), which reported that the strength of evidence is weak at this time. As some of these medications may have adverse effects, such as mental sedation or respiratory compromise, use in routine management should be tempered by the knowledge that the proven evidence of benefit relative to placebo is limited.

A recent review by Feliciano et al. (2021) meta-analyzed studies irrespective of the type of agent and its intent. While this may seemingly overcome the concerns around statistical power, it is important to differentiate between different intents for agents — use of opioids in the prophylaxis of exertional dyspnea is noticeably different from the use of opioids for the treatment of acute dyspnea in hospitalized patients. Combined analysis may lead to an imprecise and inaccurate effect estimate.

We, therefore, encourage further trials investigating pharmacologic interventions for cancer-related dyspnea. Specifically, more high-quality studies are needed that have a larger sample size, carefully defined roles of pharmacologic agent and patient population (i.e., separating opioids for prophylaxis of exertional dyspnea from treatment of acute dyspnea in hospitalized patients), identified patient subgroups that may be more likely to experience benefit, and multicentered in study design. Greater funding in this field will likely be needed to support the undertaking of these trials.

This study has several major limitations. As previously mentioned, limited statistical power led to no indirect comparisons. This study, therefore, adopts a network meta-analysis methodology, but it cannot deliver all the results typically associated with a network meta-analysis. Furthermore, as is the nature with systematic reviews, the strength of the review's conclusion relies on the strengths and any limitations reported within the individual studies. Given the small literature base, definitive conclusions cannot be drawn from this review at this time. This review should serve as motivation for larger trials to provide a better understanding of the efficacy of pharmacologic treatments in the setting of cancer-related dyspnea.

In summary, no conclusions can be drawn from the current limited literature base on cancer-related dyspnea. The use of pharmacologic interventions that may have important adverse effects relative to placebo should be used cautiously or within the context of a trial. Morphine sulfate may be better at controlling everyday dyspnea than placebo. Further trials are needed to report on the efficacy of pharmacologic interventions for the prophylaxis and treatment of cancer-related dyspnea.

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Conflicts of interest. The authors declare that they have no conflict of interest.

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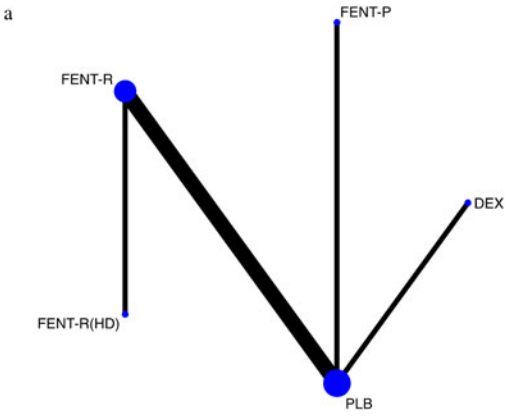
Appendix 1. Search Strategy

PubMed (769 results)
(dyspnea[mh] OR dyspnea[tw] OR dyspnoea[tw])
AND
(cancer[sb] OR neoplasms[mh])
AND
(pharmacologic*[tw] OR pharmacologic actions[mh] OR corticosteroid*[tw] OR benzodiazepine[mh] OR benzodiazepine*[tw] OR opioid*[tw] OR analgesics, opioid[mh] OR puffer*[tw] OR atrovent[tw] OR chlorpromazine[mh] OR chlorpromazine[tw] OR phenothiazines[mh] OR drug therapy[sh])
AND
(randomized[tw] OR randomised[tw] OR randomized controlled trial[pt] OR cohort[tw] OR case-control*[tw] OR controlled clinical trial[pt])

Embase (636 results) and Cochrane (39 results)
(exp dyspnea/ or dyspnea.mp. or dyspnoea.mp.)
and
(cancer.mp. or exp malignant neoplasm/ or exp neoplasm/)
and
(pharmacologic*.mp. or exp drug mechanism/ or exp corticosteroid/ or corticosteroid*.mp. or exp benzodiazepine/ or benzodiazepine*.mp. or opioid*.mp. or exp opiate/ or puffer*.mp. or atrovent.mp. or exp chlorpromazine/ or chlorpromazine.mp. or phenothiazines.mp. or exp phenothiazine derivative/ or exp drug therapy/)
and
(exp randomized controlled trial/ or randomized.mp. or randomised.mp. or exp cohort analysis/ or exp controlled study/ or cohort.mp. or exp case control study/ or case-control*.mp. or controlled clinical trial.mp. or exp controlled clinical trial/)
Limits: Limit to Cochrane Library, and Exclude Medline journals

Appendix 2. Network Meta-Analysis Map

(a) Prophylaxis for Exertional Dyspnea



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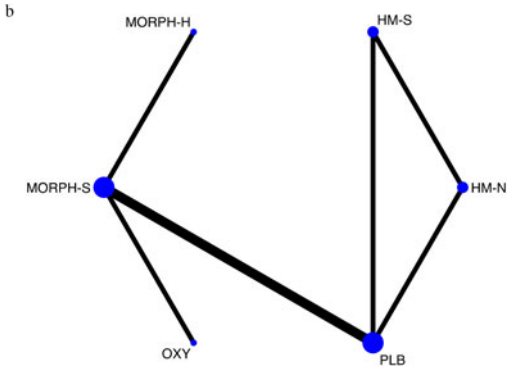
(b) Treatment of Everyday Dyspnea



Legend:
DEX, dexamethasone;
FENT-P, fentanyl, parenteral;
FENT-R, fentanyl, rapid onset;
FENT-R(HD), fentanyl, rapid onset, high dose;
HM-N, hydromorphone, nebulized;
HM-S, hydromorphone, systemic;
MORPH-H, morphine, hydrochlorate;
MORPH-S, morphine, sulfate;
OXY, oxycodone, oral;
PLB, placebo.

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