UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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TODAY'S TOPIC:

Opioids for Dyspnea: Review of the Evidence

Background:

Dyspnea is the feeling of breathlessness and it affects many patients with serious illness, especially those with cancer, heart or lung disease. Several nonpharmacologic strategies have been found to be helpful to relieve dyspnea symptoms including the use of a bedside fan, breathing exercises, and supplemental oxygen (if hypoxic). Opioids continue to have the most evidence to support their use for dyspnea, although depending on the underlying serious illness contributing to the dyspnea, evidence is slightly mixed. Proposed mechanism for the use of opioids for dyspnea include: decreasing respiratory drive, altering central perception, and altering peripheral opioid receptors within the lungs. Less evidence is available overall for the use of benzodiazepines or nebulized medications.

Importance:

Many of our patients experience dyspnea because of their life-limiting illness. It is important for palliative care clinicians to know the data behind opioid use for dyspnea.

The Literature:

J Palliat Med. 2023 May;26(5):711-726.

Opioid management of dyspnea at end of life: A systematic review

Methods: Literature search from January 1, 2000 to December 23, 2021; opioids for dyspnea within last 30 days of life; excluded case reports, book chapters, conference abstracts and non-English publications

Results: n=23 studies

- Patients with lung cancer, interstitial PNA, interstitial lung disease, end-stage heart failure, or chronic obstructive pulmonary disease
- Dyspnea assessment occurred through self-reporting tools such as visual analog scale (VAS), numeric rating scale (NRS), Modified Borg Scale, Palliative care outcomes collaboration (PCOC), mild-severe categorical scale, as well as proxy reporting tools/methods through retrospective chart reviews, observer three-grade rating
    - Different opioid regimens evaluated: N=13 morphine, N=6 fentanyl, N=5 oxycodone, N=2 hydromorphone
        - Utilized difference doses, formulations and outcomes (safety vs. efficacy)
        - Most frequently used route of administration was: parenteral, followed by oral, a combination, and nebulization
        - Difficult to compare studies in this way
        - Overall, mixed results
- Adverse effects: 10/23 studies did not report any opioid-associated adverse effects
    - No reported respiratory rate decreases in studies using low dose intermittent opioid dosing
        - One study utilizing continuous morphine infusion had 1 instance of respiratory depression, although resolved when infusion rate was decreased
    - Drowsiness/somnolence was the most frequently reported adverse effect, typically when parenteral opioids are used
- Bias risk: only 2 studies included were controlled trials with low to moderate risk of bias; out of the remaining 21 studies, 8 had a serious risk of bias and 11 had a critical risk of bias

Conclusion: "Lack of consistent evidence in the current literature surrounding end-of-life opioid use for dyspnea and does not permit an overall conclusion on opioid selection, route of administration, and dosing"

J Pain Symptom Manage. 2023 May;65(5):400-408.

Systemic opioids for dyspnea in cancer patients: A real-world observational study

Objective: To evaluate the effectiveness and safety of systemic regular opioids for dyspnea in cancer patients, in a real-world palliative care setting

Methods: multicenter, prospective observational study, enrolled adult patients with cancer who Started regular opioids for dyspnea from 12 palliative care services (PC units or consultation teams)

- T1: 24 hours, T2: 48 hours, and T3: 72 hours
- Exclusion: patients receiving steroids for COPD exacerbation or those receiving antibiotics for PNA or patients undergoing interventions that might provide short-term change in dyspnea (eg. pleural effusion drainage)

Results: n=402, mean age 79.4 (SD: 12.6), 54/7% male, most common primary cancer site was lung, 51/5% had lung metastases, 63.2% had pleural effusion, 55.7% opioid naïve

- Opioid tolerant patients have baseline opioid dose of 55.7mg OME/day, 26.4% switched opioids for dyspnea management
- Opioid doses, routes were not specified
- The proportion of responders increased NRS: 68.8% (95%CI: 0.63−0.74) at T1 to 82.1% (95%CI: 0.76−0.87) at T3 and IPOS: increased from 42.5% (95%CI: 0.38−0.48) at T1 to 57.0% (95%CI: 0.51−0.63) at T3

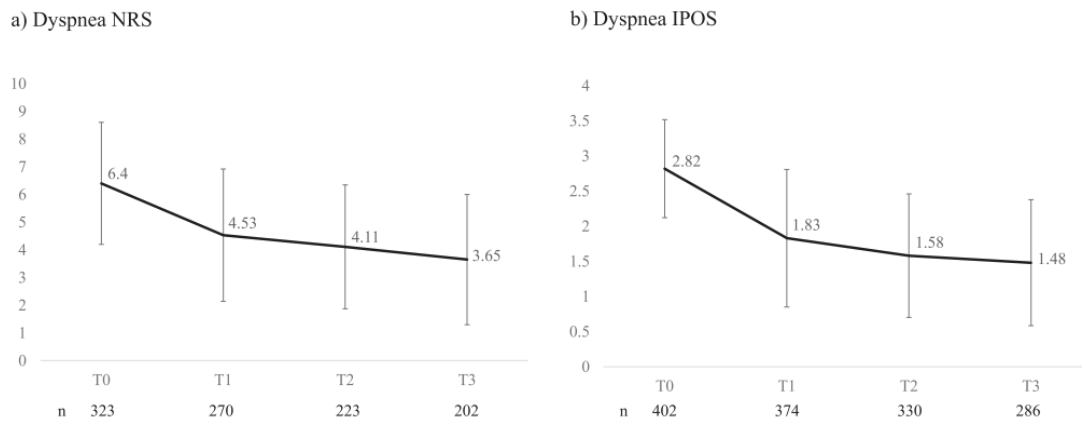

Fig. 3. Changes in dyspnea intensity with time.

- Factors influencing the response to opioids for dyspnea : opioid-naïve, absence of liver mets, prognosis of weeks or months, and severe levels of dyspnea (NRS ≥ 6)
- Safety: most common ADE was somnolence occurring in 25-30% of group over the three time periods

Conclusion: Regular systemic opioids were effective for dyspnea in real-world cancer patients receiving palliative care services

CLINICAL PEARL: It is important to consider patient-specific factors to weigh risks and benefits of opioid therapy prior to opioid selection and initiation for dyspnea.

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Thorax. 2020 Jan;75(1):50-56.

Regular, sustained release morphine for chronic breathlessness: A multicentre, double-blind, randomized, placebo-controlled trial

Methods: phase III, multicenter, double-blind, randomized, parallel-arm trial

- Morphine SR 20mg PO versus placebo x 7 days, with the ability to take morphine 2.5mg Q4H PRN
    - Inclusion: adult patients with chronic breathlessness from cancer, COPD, CHF, mixed or other with modified Medical Research Council (mMRC) breathlessness score of ≥ 2, stable medications for breathlessness for the previous week except 'as needed' medications
    - Exclusion: treatment with ≥ 20mg oral morphine equivalent per day in the 7 days before screening , Australia-modified Karnofsky Performance Status (AKPS) scale < 40, CrCl < 25mL/min, liver dysfunction (defined in the study methods),

Results:

- Efficacy

Table 2 Treatment effects of sustained-release morphine 20 mg/day versus placebo from baseline to days 5–7 or end of treatment in the intention-to-treat population (n=284)

	Morphine 20 mg/day (n=145)	Placebo (n=139)	Morphine versus placebo	
	Mean change from baseline (SE)		Mean difference (95% CI)	P value
Primary endpoint				
Breathlessness now (VAS)	−5.00 (2.13)	−4.86 (2.07)	−0.15 (−4.59 to 4.29)	0.95
Secondary endpoints				
Worst breathlessness, 24 hours (VAS)	−10.51 (2.59)	−5.29 (2.61)	−5.23 (−10.77 to 0.31)	0.064
Best breathlessness, 24 hours (VAS)	−2.11 (2.14)	0.80 (2.10)	−2.91 (−7.43 to 1.61)	0.207
Average breathlessness, 24 hours (VAS)	−4.49 (2.09)	−2.36 (2.06)	−2.13 (−6.64 to 2.38)	0.355
Breathlessness unpleasantness now (VAS)	−2.16 (2.21)	0.10 (2.20)	−2.26 (−6.87 to 2.36)	0.338
Change in participant functional status (AKPS)	−1.15 (0.75)	−0.26 (0.75)	−0.89 (−2.44 to 0.66)	0.260
Participant health-related quality of life (EORTC-QLQ-C15 PAL)	1.8 (2.2)	1.5 (2.2)	0.35 (−4.41 to 5.11)	0.88
Appetite loss (EORTC-QLQ-C15 PAL)	3.0 (3.2)	0.5 (3.2)	2.46 (−4.22 to 9.14)	0.47
Constipation (EORTC-QLQ-C15 PAL)	15.8 (3.8)	2.3 (3.8)	13.47 (5.31 to 21.62)	0.001
Dyspnoea (EORTC-QLQ-C15 PAL)	−7.0 (2.9)	−5.9 (2.8)	−1.08 (−7.14 to 4.98)	0.73
Emotional functioning (EORTC-QLQ-C15 PAL)	−0.8 (2.3)	2.2 (2.3)	−3.08 (−7.97 to 1.81)	0.215
Fatigue (EORTC-QLQ-C15 PAL)	6.1 (2.9)	−4.8 (2.9)	10.92 (4.78 to 17.06)	<0.001
Nausea/vomiting (EORTC-QLQ-C15 PAL)	6.1 (2.6)	−1.4 (2.6)	7.51 (1.98 to 13.04)	0.008
Pain (EORTC-QLQ-C15 PAL)	−1.1 (2.4)	0.02 (2.4)	−1.12 (−6.28 to 4.05).	0.67
Physical functioning (EORTC-QLQ-C15 PAL)	−5.0 (2.3)	−0.6 (2.4)	−4.42 (−9.43 to 0.59)	0.083
Insomnia (EORTC-QLQ-C15 PAL)	−6.1 (3.5)	−8.4 (3.4)	2.27 (−5.10 to 9.64)	0.54
Carers quality of life (CQOLC)	−1.4 (2.3)	−2.4 (3.2)	0.94 (−7.70 to 9.58)	0.82
Blinded treatment preference				
I have been less breathless during the past week	64/132 (48.5%)	66/134 (49.3%)	N/A	N/A
This medication would benefit me enough to be on it long term	55/128 (43.0%)	62/131 (47.3%)	N/A	N/A

AKPS, Australia-modified Karnofsky Performance Status; CQOLC, Carer Quality of Life Index—Cancer; VAS, 100 mm visual analogue scale.

- Safety: GI side effects (nausea/constipation) significantly worse in opioid group

Conclusion: in patients with optimally treated severe disease and chronic breathlessness, oral SR morphine daily was not observed to improve breathlessness now more than placebo but intervention arm used fewer doses of 'as needed' morphine

J Clin Oncol. 2021 Apr 20;39(12):1389-1411.

Management of dyspnea in advanced cancer: ASCO Guideline

- Summary:
    - AHRQ systematic review included 48 RCTs and 2 retrospective cohort studies
        - Most common cancers: lung cancer, mesothelioma included
        - Systematic review did not identify a benefit for opioids; significant limitations exist in the trials included. However, panel still recommends a trial given suggested benefit in other conditions with high rates of dyspnea
        - Selection of opioid should be guided by patient-specific factors, consider risk-benefit ratio prior to starting
    - Expert panel recommendations:
        - Morphine is the opioid with the most evidence to support its use for dyspnea
        - Consider using PRN opioids for acute dyspnea in the hospital and ambulatory patients with activity-induced dyspnea. Consider scheduling opioids (ER or IR) for patients with chronic breathlessness
        - "For patients who derive inadequate relief from nonpharmacologic interventions, systemic opioids should be offered."

Chest. 2010 Mar;137(3):674-91.

American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease

- Summary:
    - Literature review retrieved 13 RCTs, 10 systematic reviews, 10 prospective studies, 7 retrospective studies, 7 case studies, and 2 topic reviews
    - Expert panel recommendations:
        - Appreciated the mixed evidence for using opioids for dyspnea in different diseases (COPD, pulmonary fibrosis, heart disease, cystic fibrosis), settings (ambulatory, end-of-life), route of opioid administration(oral, parenteral, nebulized)
        - 78% of panel agreed that patients with advanced lung and heart disease, oral and/or parenteral opioids can provide relief of dyspnea
        - 100% of the panel agreed that respiratory depression is a widely held concern with the use of opioids for dyspnea

Bottom Line:

- Mixed evidence exists for the use of opioids for dyspnea
- This is likely because variety exists within the populations (cancer, CHF, COPD, etc), chronicity of breathlessness, opioid selection, opioid dose, opioid formulation.
- It would make sense that not all dyspnea is responsive to opioids and that one size does not fit all given different etiologies of dyspnea exist.
- Low dose opioids utilized for dyspnea seem generally safe with a relatively low risk of respiratory depression based on our available evidence
- Even with limited data, it still seems reasonable to try opioids for refractory dyspnea after treating any reversible causes for dyspnea (PNA, COPD exacerbation), and nonpharmacologic options have been ineffective.
- Consider patient-specific factors and weigh risks and benefits of opioid therapy prior to selection and initiation of opioids for dyspnea.

CLINICAL PEARL: It is important to consider patient-specific factors to weigh risks and benefits of opioid therapy prior to opioid selection and initiation for dyspnea.