

Dyspnea at End of Life

Dyspnea is the most common symptom in advanced COPD and has numerous contributors and exacerbators in “the physical, psychological, interpersonal and spiritual dimensions.”¹ In advanced COPD, the disease is no longer in a modifiable state and despite maximizing inhalational therapies and non-pharmacologic methods, the dyspnea experience is often refractory. In addition to COPD, some of the common causes of dyspnea seen at end of life include, but are not limited to, heart failure, anemia, pain, anxiety, and extreme temperatures.¹

Oral & Parenteral Opioid Use for Dyspnea

Opioids, when added to standard therapy, have been shown to reduce the sensation of dyspnea. This therapy is well supported, in oral and parental form, alongside a multidisciplinary approach to gain control of this symptom when refractory to other measures.^{1,2-8}

Although appreciated that opioids produce respiratory depression as an adverse effect, the precise mechanism of how they manage breathlessness remains unclear. Opioids may diminish the chemoreceptor response to hypercapnia and hypoxia, or they may cause vasodilation, resulting in decreased dyspnea due to the resulting reduction in preload and pulmonary congestion. Additionally, opioids can facilitate a decrease in anxiety and the subjective sensation of dyspnea without reducing respiratory rate or oxygen saturation.⁹

Many clinicians use opioids as drugs of choice for dyspnea at end of life. Typically, in opioid naïve patients, the opioid is started at a low dose, such as oral morphine up to 5mg or parenteral morphine up to 2mg. These doses will usually provide relief for most patients. Patients on chronic opioids may need higher doses.²

Nebulized Opioid Use for Dyspnea

Much of the support for nebulized opioid use is anecdotal. Clinician experience varies, and it is important to recognize that, although there are a variety of small trials, case series and expert opinions in the literature, there remains no randomized, controlled studies to support this practice.

Specifically, no randomized controlled studies have demonstrated greater efficacy, or less side effects, comparing nebulized morphine to oral or parental morphine.² The one study that attempted this comparison used a limited sample size and did not have enough power to show a significant difference.¹¹ Some experts have hypothesized that nebulized opioids do not act systemically and opioids must reach systemic blood levels to reduce dyspnea.¹¹ Additionally, non-controlled trials have “consistently demonstrated a lack of effect of nebulized morphine” compared with placebo for dyspnea.¹²⁻¹⁵

Similarly, a study of nebulized and systemic hydromorphone compared to placebo, with a large enough sample size to detect an effect, found no difference between the three groups in dyspnea score 10 minutes post-treatment.^{14,16}

Nebulized fentanyl, being lipophilic, is thought to be more readily absorbed than morphine or hydromorphone; such was the basis of one study’s conclusion that it was “superior to placebo” for dyspnea in a COPD sample population.^{12,17} Fentanyl via nebulization remains an area of interest for researchers encouraging study on a larger controlled population to truly measure efficacy.¹⁷⁻²⁰

References

1. Vanston VJ, et al. UNIPAC 8: COPD, Heart Failure, and Renal Disease In: Essential Practices in Hospice and Palliative Medicine, 5th edition. Shega JW, Paniagua MA, eds. Chicago, IL: American Academy of Hospice and Palliative Medicine, Inc; 2017.
2. Weissman DE. Dyspnea at End-of-Life. Palliative Care Network of Wisconsin Fast Facts. Revised June 2024.
3. Shega JW, Paniagua MA, eds. UNIPAC 4: Nonpain Symptom Management. Essential Practices in Hospice and Palliative Medicine, 5th edition. Chicago, IL: American Academy of Hospice and Palliative Medicine; 2017.
4. Davis MP, et al. Looking both ways before crossing the street: Assessing the benefits and risk of opioids in treating patients at risk of sleep-disordered breathing for pain and dyspnea. *J Opioid Manag.* 2017;May/Jun;13(3):183-196.
5. Jennings AL, et al. A systemic review of the use of opioids in the management of dyspnea. *Thorax.* 2022; 57(11):939-944.
6. Lorez KA, et al, Evidence for improving palliative care at the end of life: A systemic review. *Ann Intern Med.* 2008;148(2):147-159.
7. Marciniuk D, et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: A Canadian Thoracic Society clinical practice guideline. *Can Respir J.* 2011;18(2):69-78.
8. Waseem A, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med.* 2011;155(3):179-191.
9. Indelicato RA. The advanced practice nurse's role in palliative care and the management of dyspnea. *Topics in Advanced Practice Nursing eJournal.* 2006;6(4).
10. Bruera E, et al. Nebulized versus subcutaneous morphine for patients with cancer dyspnea: A preliminary study. *J Pain Symptom Manage.* 2005;29:613.
11. CAPC Online Clinical Training Courses. Symptom Management: Dyspnea. Reviewed November 12, 2015.
12. Dudgeon et al. Assessment and Management of Dyspnea in Palliative Care. In: UpToDate, Bruera E, Givens J, Hollingsworth H, eds. Waltham, MA: UpToDate, Inc; Updated March 9, 2020.
13. Davis C. The role of nebulised drugs in palliating respiratory symptoms from malignant disease. *Eur J Palliat Care.* 1995; 2:9.
14. Booth S, et al. The etiology and management of intractable breathlessness in patients with advanced cancer: A systematic review of pharmacological therapy. *Nat Clin Pract Oncol.* 2008; 5:90.
15. Barnes H, et al. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev.* 2016; 3:CD011008.
16. Charles MA, et al. Relief of incident dyspnea in palliative cancer patients: a pilot, randomized, controlled trial comparing nebulized hydromorphone, systemic hydromorphone, and nebulized saline. *J Pain Symptom Manage.* 2008; 36:29.
17. Jensen D, et al. Inhaled fentanyl citrate improves exercise endurance during high-intensity constant work rate cycle exercise in chronic obstructive pulmonary disease. *J Pain Symptom Manage.* 2012; 43:706.
18. Coyne PJ, et al. Nebulized fentanyl citrate improves patients' perception of breathing, respiratory rate, and oxygen saturation in dyspnea. *J Pain Symptom Manage.* 2002 Feb;23(2):157-60.
19. Bausewein C, Simon S. Inhaled nebulized and intranasal opioids for the relief of breathlessness. *Curr Opin Support Palliat Care.* 2014 Sep;8(3):208-12. doi: 10.1097/SPC.0000000000000071.
20. Higgins EA, et al. Nebulized fentanyl for dyspnea: A retrospective chart review. *J Pain Palliat Care Pharmacother.* 2020 Jun;34(2):77-81.