



## Opioids for Breathlessness in Advanced Disease

This guideline is intended to be used to aid both primary and secondary care healthcare professionals in the use of opioids for adult patients with breathlessness in advanced disease.

### Background

- The effectiveness of opioids in relieving breathlessness has been studied among people with cancer, COPD and chronic heart failure.<sup>1</sup> Most evidence is in people with COPD.<sup>2</sup>
- Not all opioids show reduction in breathlessness. Data from larger RCTs supports **morphine but not oxycodone**.<sup>7,17</sup> Most experience is with morphine.<sup>1</sup> There is insufficient evidence as to whether the synthetic opioids (e.g. fentanyl and buprenorphine) are effective in breathlessness. There is preliminary evidence to support prophylaxis for exertion-induced breathlessness for morphine and fentanyl but the risk-benefit balance is not known, especially with longer term use.<sup>2</sup>
- Modified release preparations to acquire steady state should be used rather than immediate release in the vast majority of patients<sup>8,9</sup>
- Systematic reviews and RCT meta-analyses support use of opioids by **oral and parenteral** but not nebulized route.<sup>10,11</sup>
- Morphine and other opioids reduce the ventilator response to hypercapnia, hypoxia and exercise, decreasing respiratory effort and breathlessness.<sup>3</sup> Improvements are seen at doses that do not cause respiratory depression.<sup>4-5</sup>
- In the largest cohort study (of patients with severe COPD), there were no excess deaths or hospitalizations reported with lower opioid doses equivalent to morphine ≤30mg/24h PO. This supports limiting the dose of morphine to within this range in this group of patients in the context of appropriate monitoring.<sup>19</sup> A small number of patients with Type 2 respiratory failure may be sensitive to opioids, and a joint management plan for these individuals should be made with the Respiratory specialists. Caution is advised when patients are on other respiratory depressant medications e.g. benzodiazepines.

### Management

#### Non Pharmacological Management

[Refer to A practical guide to coping with breathlessness: Information for patients](#)

#### Pharmacological Management

Consider the use of opioids for breathlessness if:

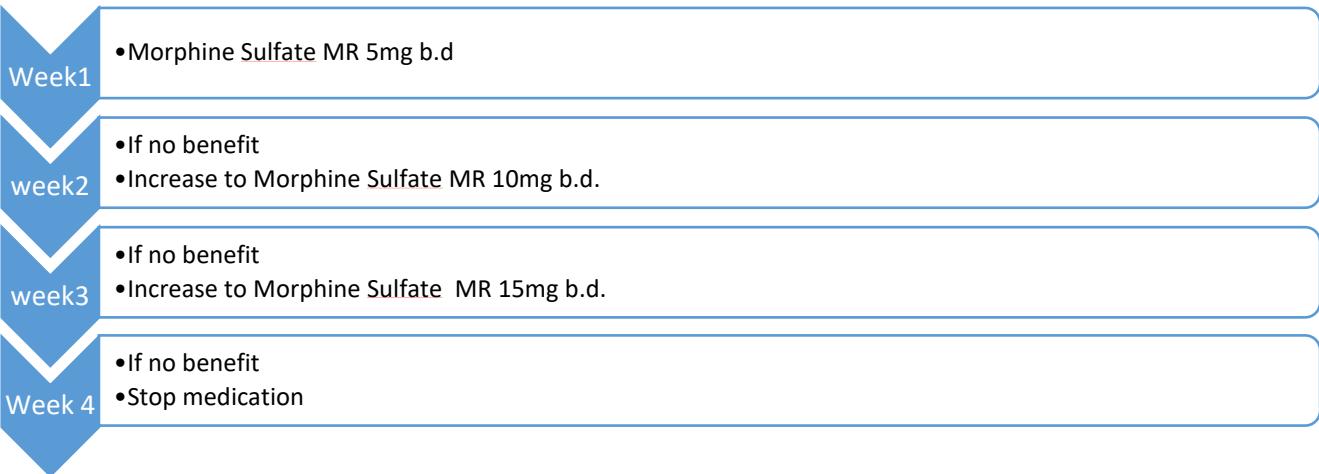
- Breathlessness persists despite optimal treatment of the underlying cause.
- Non-pharmacological methods (relevant to the performance status and prognosis of the patient) have been implemented and moderate to severe breathlessness **persists**.
- The patient has, and is using a breathless crisis plan ([Appendix 1](#)), with information for breathlessness in a format they can access.
- Opioids should only be used in the management of breathlessness in advanced disease as part of a breathlessness management plan, and not as the sole intervention/management. It cannot be assumed morphine will be beneficial in all diseases, so carefully monitoring is needed. De-prescribing should be routine in the absence of benefit in either subjective breathlessness or performance status.

Caution: Short term opioid related adverse effects are generally mild and include constipation; nausea the latter is mostly self-limiting. It is important to provide appropriate explanation, laxatives (regular), and antiemetic (p.r.n.) and monitoring.<sup>1</sup> Opioids can cause a range of adverse effects on immune and endocrine function, and these are likely to become more clinically relevant with long term use, **so careful thought should be given to long term opioid prescribing in patients with longer prognoses (e.g. >12 months)**.



## Starting morphine for breathlessness in opioid-naïve patients with normal renal function

### Modified -release (MR) approach



### Immediate-release (IR) approach

MR morphine sulfate should be the standard approach. For the small group of patients who don't wish to take MR opioids, IR could be considered. Starting doses can be as little as 500 micrograms morphine sulfate b.d., titrated gradually weekly up to 5mg q.d.s., if necessary. When dose is unchanged for 2 weeks, consider switching to MR formulation.<sup>1</sup>

### Already taking an opioid

In patients on <30mg/24h oral morphine (or oral morphine equivalent) for pain, the dose can be increased in appropriate increments up to 30mg total daily dose. In patients taking doses > 30mg/24h oral morphine (or oral morphine equivalent) for other indications, there is unlikely to be any benefit to starting additional opioids for breathlessness.

### Renal impairment

Due to the lack of evidence for oxycodone continue to use Morphine between a GFR of <50 and >20 but titrate more slowly and monitor closely for side effects. If GFR <20, a trial of low dose buprenorphine may be considered. If concerns seek specialist advice.

### Breathlessness in the last days and hours of life

The recommended daily limits to opioid dose may not apply in the last days of life. For LTHT patients: See [LTHT Care of the Dying Person](#) - (Breathlessness) or seek SPCT advice. For Hospice, Community Patients [Care of Dying Person -Breathlessness](#)

### Key Points

- There is evidence that opioids are safe in breathless patients when used appropriately, and at low doses.
- Morphine is the opioid with the best evidence for breathlessness.
- Use MR preparations where at all possible.
- Use the lowest effective dose and stop medication that is not helping.
- Use more sparingly in patients with longer prognoses due to accumulation of increasing adverse effects over time
- Try and avoid complicated regimes of differing opioids and doses for different indications, but consider the whole clinical picture.
- Medication alone is unlikely to be fully effective for breathlessness and should be one part of a multi-faceted approach.



## Provenance:

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**Clinical Condition** - Breathlessness

**Target Patient Group** - Adults with advanced disease

**Target Professional Group** -

- Primary & Secondary Care Healthcare Professionals

### References:

- <sup>1</sup>Wilcock A et al. (2020). Palliative Care Formulary 7ed: Morphine for Breathlessness. Pharmaceutical Press. London
- <sup>2</sup>Johnson MJ, Currow D. (2020). Opioids for breathlessness: a narrative review. *BMJ Supportive & Palliative Care*. **10**: 287-295
- <sup>3</sup>Twycross R and Wilcox A (ed.). (2016). Introducing Palliative Care 5ed. Palliative.drugs.com. Nottingham p.145-155
- <sup>4</sup>Lopez-Saca JM and Centeno C. (2014). Opioids prescription for symptoms relief and the impact of respiratory function: updated evidence. *Current Opinion in Supportive and Palliative Care*. **8**: 383-390.
- <sup>5</sup>Verberkt CA et al. (2017). Respiratory adverse effects of opioid for breathlessness for breathlessness: a systematic review and meta-analysis. *European Respiratory Journal*. **50**: 1701153
- <sup>6</sup>Ferreira DH, Louw S, McCloud P, et al. (2020). Controlled-release oxycodone vs. placebo in the treatment of chronic Breathlessness-A multisite randomized placebo controlled trial. *J Pain Symptom Manage*. **59**:581-9
- <sup>7</sup>Ekström M, Nilsson F, Abernethy AA, et al. (2015). Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thorac Soc*. **12**:1079-92.
- <sup>8</sup>Hayen A, Wanigasekera V, Faull OK, et al. (2017). Opioid suppression of conditioned anticipatory brain responses to breathlessness. *Neuroimage*. **150**:383-94
- <sup>9</sup>Barnes H et al. (2016). Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database of Systematic Reviews*. **3**: cd11008.
- <sup>10</sup>Ekstrom M et al. (2018). One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax*. **73**: 88-90 <sup>12</sup>
- Cohen M et al. (1991). Continuous intravenous infusion of morphine for severe dyspnoea. *Southern Medical Journal*. **84**: 229-234.
- <sup>11</sup>Boyd K and Kelly M (1997) Oral morphine a symptomatic treatment of dyspnoea in patients with advanced cancer. *Palliative Medicine*. **11**: 277-281
- <sup>12</sup>Abernethy A P et al. (2003). Randomised, double blind, placebocontrolled crossover trial of sustained release morphine for the management of refractory dyspnoea. *British Medical Journal*. **327**: 523-528
- <sup>13</sup>Allen S et al. (2005). Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end stage idiopathic pulmonary fibrosis. *Palliative Medicine*. **19**: 128-130.
- <sup>14</sup>Rocker GM et al. (2013). Opioid therapy for refractory dyspnoea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *Canadian Medical Association Journal Open*. **1**: E27-36
- <sup>15</sup>Currow DC, McDonald C, Oaten S et al. (2011). Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage*. **42**:388-99.
- <sup>16</sup>Johnson MJ, Sbizzera I, Fairhurst C, et al. (2020). No excess harms from sustained-release morphine: a randomised placebocontrolled trial in chronic breathlessness. *BMJ Supportive & Palliative Care*. **10**:421-428.
- <sup>17</sup>Ekstrom M P, Bornefalk-Hermansson A, Abernethy A P, Currow D C. (2014). Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study BMJ: 348

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