

## The use of opioids in late-stage COPD—Where are we now?

Chronic breathlessness is defined as breathlessness that persists on minimal or no exertion despite the optimal treatment of the underlying disease and other contributing factors.<sup>1</sup> It is a cardinal and prevalent symptom of late-stage chronic obstructive pulmonary disease (COPD). Chronic breathlessness is present in about 40% of people with COPD in high-income countries, worsening with age and severity of disease. The majority of people with late-stage COPD experience such breathlessness. COPD is also associated with a high frequency of comorbidities.<sup>2</sup> Common symptoms related to COPD and its systemic manifestations include, but are not limited to, long-term pain, sleep disturbance, fatigue and cough. This paper focuses on chronic breathlessness.

In COPD at a population level, breathlessness is more strongly associated with mortality than the measurable degree of airway obstruction.<sup>3,4</sup> There is also a relatively poor correlation between pulmonary function tests and the subjective assessments of chronic breathlessness. Other population-level associations with chronic breathlessness include poorer quality of life (physical and mental components)<sup>5</sup>; greater anxiety and depression; poorer workforce participation in people of working age; greater disability measured on the World Health Organization Disability Assessment Schedule (WHO-DAS); poorer perceived health; less sexual activity; and a smaller Life-Space geographic footprint.

In symptom management, the first step in managing chronic breathlessness requires clinicians to ensure that reversible causes are optimally treated. More than one underlying aetiology often contributes to chronic breathlessness and all need to be addressed in each person's management plan. Non-pharmacological interventions include pulmonary rehabilitation, activity pacing, and a handheld battery-operated fan.<sup>6</sup> Despite these measures, many people still require pharmacotherapy for the symptom, especially in late-stage disease.

Several medications have been assessed in adequately powered studies, yet the only class of medications, to date, which has an evidence base is opioids. There are two main sources to inform clinical considerations of effectiveness of opioids for the symptomatic reduction of chronic breathlessness: meta-analyses; and adequately powered studies.

A sub-group analysis of people with COPD and breathlessness in a recent meta-analysis of opioids administered long enough to reach steady state ( $n = 91$ ) found an overall

### Key points

- The use of regular, low-dose morphine to reduce symptomatic chronic breathlessness was identified in a systematic review and meta-analysis.
- Since that meta-analysis, three adequately powered studies have not confirmed its findings in people with moderate to severe chronic breathlessness.
- Two of those subsequent studies identified that people with COPD and severe breathlessness (housebound or breathless when dressing or undressing) may derive symptomatic benefits safely.
- A short trial (1 week) of regular, low-dose, sustained-release morphine (10 mg/24 h) can be considered in such patients.

benefit favouring morphine over placebo.<sup>7</sup> This suggests that there is a cohort who likely derive meaningful symptomatic benefit.

Since the publication of that study, three large randomized, placebo-controlled studies have been reported ( $n = 284$ ;  $n = 156$ ;  $n = 111$ ).<sup>8–10</sup> Each had differing primary endpoints at different times (intensity of *worst breathlessness* at 1 week,<sup>9</sup> intensity of *breathlessness now* at 1 week),<sup>8</sup> and COPD Assessment Test (CAT) scores and PaCO<sub>2</sub> at 4 weeks.<sup>11</sup> Breathlessness remained unchanged in all three studies, however, two of the three studies reported sub-group analyses that described sub-populations that derived significant benefit. The study by Verberkt et al. found two significant improvements in its secondary outcomes: *worst breathlessness* at 28 days after commencing the study; and a difference between the active and placebo arms for the CAT score. The study by Ferreira et al. identified that people with the most severe breathlessness (mMRC<sup>3,4</sup>) and COPD achieved significant clinical benefit.<sup>12</sup>

Accurately identifying patient characteristics that predict a beneficial response to regular, low-dose, sustained-release morphine remains a challenge for researchers and clinicians. Basic clinico-demographic factors have been defined in two studies using data from double-blind, placebo-controlled,

randomized controlled trials.<sup>13,14</sup> In the study by Johnson et al. from four clinical studies of morphine for the symptomatic reduction of breathlessness ( $n = 213$ ), baseline predictors of a greater likelihood of response included more intense breathlessness and younger age.<sup>14</sup> Body mass index (BMI) was not available in this study. In the study by Verberkt et al., 21 participants in the active arm of their parallel arm clinical trial had a  $\geq 1$  point improvement on a 0–10 numerical rating scale.<sup>13</sup> The two baseline predictors of response were higher baseline intensity of breathlessness and higher BMI. Age was not a predictor in this study.

To date, exploring key single nucleotide polymorphisms (SNPs) relating to opioid metabolism, transport or receptors has not found predictors of response.<sup>15</sup>

There appear to be a group of people (who are yet to be characterized from their pre-treatment characteristics) who have a marked benefit from regular, low-dose, sustained release morphine. The benefits are described by trial participants as ‘life-changing’ and persisted for at least 6 months with no increase in morphine dose.<sup>16</sup> Although there are small numbers who describe benefits of this magnitude, the benefits were further reflected in improved actigraph-measured activity and increased Global Impression of Change scores.

Opioids for pain have a wide therapeutic index. Morphine for the symptomatic reduction of chronic breathlessness may have a far narrower window for net benefit. Many people reflect that even mild adverse events negate any symptomatic reduction in chronic breathlessness.<sup>17</sup> In a meta-analysis of 64 studies, of which five had data on safety measures, Verberkt et al. found no evidence of rising carbon dioxide partial pressures nor of any drop in oxygenation—two principal concerns when prescribing opioids for people with COPD.<sup>11</sup> A pre-planned secondary analysis of the BEAMS study found that daytime drowsiness was no worse in the morphine arm than placebo and that, at 4 weeks, participants who reported reduced breathlessness with morphine also had improvement in Leeds Sleep Evaluation Questionnaire (LSEQ) domain scores including perceived sleep quality and daytime functioning.<sup>18</sup>

However, objective assessment of the effects of low-dose, slow-release morphine during sleep in people with COPD and chronic breathlessness has identified that although there is no negative effect on next-day alertness (including driving simulator performance), morphine causes lighter sleep depth, higher mean and peak transcutaneous CO<sub>2</sub> and lower oxygen saturations.<sup>18,19</sup> The longer-term consequences of these changes are yet to be determined.

Of note, any therapeutic benefit does not seem to have a whole-of-class effect for opioids. Studies utilizing oxycodone do not seem to have any signal of symptomatic benefit. Interestingly, it may also be that not all underlying aetiologies of chronic breathlessness derive the same benefits. One study in pulmonary artery hypertension saw no signal of benefit in the primary nor secondary outcomes and another in interstitial lung disease.<sup>20</sup>

At present, data from a meta-analysis and two large, randomized, controlled studies indicate that in people with

severe chronic breathlessness secondary to COPD, a short trial of low dose, sustained release morphine is safe and potentially beneficial. When introduced at a low dose and titrated slowly (at least 1 week between commencing and titration), a sub-group of people derive significant, sometimes life-changing, benefit. Developing accurate methods to identify which patients derive benefit from regular, low-dose, sustained-release morphine is a critical goal for future research.


## KEYWORDS

chronic obstructive pulmonary disease, COPD, meta-analysis

## CONFLICT OF INTEREST STATEMENT

T.J.A. had no disclosures. D.C.C. is an Advisory Board member and consultant for Helsinn Pharmaceuticals; consultant and receives payment for intellectual property with Mayne Pharma International Pty Ltd.; subcontractor to Nous Group Pty Ltd.; Board member for icare Dust Diseases Care NSW; Board member/Director NSW Health Pathology; Board member/Director for Chris O’Brien Lifehouse Cancer Centre.

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