

# Opioids for dyspnoea

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Opioids have a role in the treatment of severe dyspnoea, but careful monitoring of their effects is essential.

To understand, define, and treat dyspnoea is difficult. It is an underappreciated problem in respiratory medicine, cardiology, and palliative medicine, and it is often hard to know when to supplement the treatment of an underlying disease by pure palliation. In this issue of *Thorax* Jennings *et al*<sup>1</sup> present a meta-analysis of randomised controlled trials of opioids as treatment for dyspnoea, which shows that opioids do reduce dyspnoea in a variety of settings, including chronic obstructive pulmonary disease (COPD) and cancer. What inferences for clinical practice in primary care, secondary care, or specialist palliative care can be drawn from this finding? And what impact ought it to have?

## BACKGROUND

Dyspnoea is a perception, and perceptions are affected by more than physiological variables. Although simple statements such as “dyspnoea is an uncomfortable sensation of breathing”<sup>2</sup> may suffice as a shorthand definition of dyspnoea, the American Thoracic Society has suggested the following broader description: “. . . dyspnoea is a term used to characterise a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors that may induce secondary physiological and behavioural responses”.<sup>3</sup> It therefore follows that methods of treating dyspnoea could include reducing the metabolic demand for ventilation, increasing the efficiency of the respiratory system as a gas exchanger, decreasing central respiratory drive, or reducing the perception of dyspnoea. This itself could include diminishing or altering psychosocial factors as well as pharmacological treatment.

Opioid treatment for the relief of dyspnoea is thus only one of many treatments available, with other examples being supplemental oxygen,<sup>4</sup> chest wall vibration,<sup>5</sup> pulmonary rehabilitation including lifestyle modification,<sup>6</sup> cognitive and behavioural treatment,<sup>7</sup> or facial cooling.<sup>8</sup>

Why should opioids reduce dyspnoea? Do they have an effect that is separate

and different from their effect on pain perception? Recent brain imaging studies are relevant. Peiffer *et al*<sup>9</sup> studied eight healthy male volunteers and subjected them to loaded breathing to induce acute dyspnoea up to grade 5 on the Borg scale. At the same time the volunteers had repeated CT-PET brain scans. Neural activity (measured indirectly by this technique as locally increased cerebral blood flow) was increased in proportion to the respiratory loading in three main areas—the right anterior insula, the cerebellar vermis, and the medial pons. However, the right posterior cingulate gyrus was activated in proportion to perceived dyspnoea (and not to the inducing load). The authors hypothesised, as did Banzett *et al*<sup>10</sup> using a different experimental model, that the perception of dyspnoea, in this model at least, occurs in the insula where neural activity is proportional to the stimulus, whereas the intensity of the perception is modulated in the right posterior cingulate gyrus where other neural inputs come into play. Modulating factors might include emotions, cognitive factors, or treatments such as facial cooling which appear to reduce dyspnoea without affecting the breathing pattern.

Fascinatingly, the same areas of the brain have been shown to be activated in studies of acute<sup>11</sup> and chronic<sup>12</sup> pain. Although opioid receptors are found throughout the central nervous system, pain relief from opioids is thought to depend predominantly upon central opioid receptors rather than on peripheral receptors. It is therefore reasonable to hypothesise that exogenous opioids reduce dyspnoea by an action analogous to pain relief, where they are probably acting on receptors in the right posterior cingulate gyrus to modulate the perception of dyspnoea without necessarily altering either the drive to ventilation or the ventilation response itself.

It is important to note that this analysis helps to explain how opioids can reduce dyspnoea without changing blood gas tensions. In larger doses the mechanism of dyspnoea relief by opioids probably includes the additional effect of a direct reduction in ventilatory drive via an action on the medullary respiratory centre, together with a reduction in conscious level.

## THE META-ANALYSIS

In their meta-analysis Jennings *et al*<sup>1</sup> used Cochrane collaboration methodology. They considered only randomised, double blind, placebo controlled trials of opioids for the reduction of dyspnoea from any cause. Eighteen trials were identified and the meta-analysis showed a significant positive effect of opioids on dyspnoea with a standardised mean difference (SMD) of  $-0.31$  (95% CI  $-0.5$  to  $-0.13$ ),  $p < 0.0008$ . However, the benefits were confined to studies using oral or parenteral opioids.<sup>9</sup> The three studies of nebulised opioids included in the meta-analysis failed to show a significant effect (SMD  $-0.11$ , 95% CI  $-0.32$  to  $0.1$ ). Of the nine studies involving the use of oral or parenteral opioids included in the analysis, seven were in COPD, three using dihydrocodeine, two morphine, and two oral diamorphine. Only one study was in cancer (using subcutaneous morphine)<sup>13</sup> and one was in congestive cardiac failure using dihydrocodeine.<sup>14</sup> Although the pooled results were significant, the authors point out that the clinical effect sizes in these studies were small. The study by Johnson *et al*<sup>15</sup> was the equivalent of only 8 mm on a 100 mm Likert visual analogue scale. At the doses studied, no deleterious effects of opioids were noted on arterial blood gas tensions. The review was unable to comment on the possibility that larger doses would have produced a bigger effect, perhaps at the expense of reducing ventilatory drive and worsening blood gases as would be expected from everyday clinical experience. Furthermore, a large intersubject variability in the response to opioids seems likely.

## CLINICAL APPLICATION

When and how should opioids be used to relieve dyspnoea? It is helpful to consider the management of dyspnoea at three different stages of disease according to the severity and reversibility of the underlying cause.

Mild dyspnoea accompanying reversible disease such as moderate congestive cardiac failure is best managed by treating the cause. Any psychosocial and other non-pharmacological factors are usually straightforward to manage. Moderate and severe dyspnoea is more problematic. In such situations it is usual to continue quite intensive disease modifying treatment—for example, nebulised bronchodilators for COPD—but in the knowledge that they may be only marginally effective. Continuing dyspnoea with its associated anxiety and poor quality of life is common. If a review reveals no additional co-existing conditions which can be reversed, then non-pharmacological measures to reduce dyspnoea should probably be tried first. Good examples are pulmonary rehabilitation for COPD and probably other respiratory diseases<sup>6</sup> and cognitive therapy

for cancer. The study by Bredin *et al.*<sup>16</sup> for example, showed that in a non-blind randomised trial of lung cancer patients attending a nurse led breathlessness clinic, the treated group had a two stage increase in their performance status scale readings. (The components of the clinical care which led to this improvement are not known.)

Assessing the role if any for the pharmacological treatment of dyspnoea in these patients is much more difficult. Oxygen, sedatives, and opioids have to be considered. A detailed discussion of their relative merits is beyond the scope of this article but, in general, for most ambulant but breathless patients the evidence suggests that all three modalities may help in individual cases. Patients hypoxic on exertion may benefit from concurrent oxygen therapy.<sup>17</sup> Anxiolytics such as diazepam, methotrimeprazine, or other phenothiazines have not been shown to be consistently helpful with the side effects of drowsiness often outweighing or counterbalancing a small reduction in dyspnoea.<sup>18</sup> Exercise tolerance has not been shown to be increased.<sup>19</sup> For opiates the meta-analysis suggests that there may be a small benefit but it is important to note that a dose increase of, for example, more than 30 mg dihydrocodeine four hourly may not be useful. This is an area where the patient's needs—for example, either an increase in exercise tolerance or a decrease in dyspnoea—have to be carefully thought about and an “N of 1” trial started. Drugs should be withdrawn if they have no benefit. Assessment needs to be a specialist function and should not be undertaken without facilities such as oxygen saturation measurement and some attempt at a subjective measurement such as a visual analogue score or an objective measurement of, for example, exercise tolerance. More research in this area is needed, particularly in the use of oxygen treatment.

For the patient who is breathless at rest with very restricted mobility or distressed by breathlessness at rest and with a very short prognosis, pharmacological treatment is necessary. One randomised controlled trial<sup>13</sup> examined by Jennings *et al* showed that, in 10 cancer patients in whom the pain was controlled by morphine, a subcutaneous dose of morphine 50% greater than the pain

relieving dose produced a 50% reduction in perceived dyspnoea compared with placebo. Oxygen saturation and respiratory rate were unchanged. A similar study has not been done in patients with end stage COPD or restrictive lung disease. An uncontrolled study by Cohen *et al.*<sup>20</sup> found a similar effect from an infusion of opioids in patients with advanced lung cancer. They used bolus doses of 1–2 mg intramuscular morphine every 5–10 minutes until relief was reported, followed by a subcutaneous infusion with the hourly dose being equivalent to half the cumulative bolus dose. Six of their eight patients were better, but untoward sedation led to the dose being reduced by 50% in some. These patients had a very short life expectancy, some of them dying within 30 hours.

If anxiety is a component of terminal disease, and it often is, it seems logical to add an anxiolytic such as midazolam 5–10 mg per 24 hours or levomepromazine to the infusion. This compassionate approach is justified by the evidence we have and fits in with consistent clinical experience of the benefits of opioids in these circumstances.

A particular clinical problem which is often difficult to resolve is identifying and treating the non-cancer patient who has reached this point in his or her disease trajectory. The specialties of palliative medicine and respiratory medicine still have much to learn from each other, particularly in this respect, now that the role of palliative medicine is being expanded to the care of patients with non-cancer diseases.

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