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CLINICAL PERSPECTIVES

Management of refractory breathlessness with morphine in patients with chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive, incurable illness, which leads to significant morbidity over long periods of time and mortality. Treatment aims to reduce symptoms, improve exercise capacity and quality of life, reduce exacerbations, slow disease progression and reduce mortality. However, breathlessness is common in patients with advanced COPD and remains undertreated. As all reversible causes of breathlessness are being optimally managed, consideration should be given to specific non-pharmacological and pharmacological treatment strategies for breathlessness. Low dose morphine has been shown to reduce safely and effectively breathlessness in patients with severe COPD and refractory dyspnoea. However, despite numerous guidelines recommending opioids in this clinical setting, many barriers limit their uptake by clinicians. Integration of palliative care earlier in the disease course can help to improve symptom control for people with severe COPD and refractory breathlessness. A multidisciplinary approach involving both respiratory and palliative care teams offers a new model of care for these patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is an incurable, progressive illness characterised by airflow obstruction and respiratory failure, which leads to significant morbidity and mortality.[1] By 2030, COPD will be the fourth leading cause of death globally.[2] In Australia, 29% of people aged over 75 years have COPD, and one in three deaths due to lung disease are attributable to COPD.[3,4]

Breathlessness is a subjective experience derived from interactions between multiple physiological, psychological, social and environmental factors.[5,6] Breathlessness

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leads to significant distress, impaired physical and mental functioning, reduced quality of life and behavioural change.[6,7] Up to 98% of patients with advanced COPD experience increasing breathlessness at rest or on minimal exertion.[7,8] When breathlessness persists at rest or on minimal exertion, despite optimal treatment of the underlying causes, it is termed 'refractory breathlessness'.[9–11]

Palliative care has well-recognised benefits and aims to improve the quality of life of patients and their families when facing life-threatening illnesses.[12] Similarly for patients with refractory breathlessness, treatment goals should be individualised and patient focused, with palliative care offered not just at the end of life, but concurrently with life-prolonging, disease-directed care.[12–14]

Refractory breathlessness by definition is difficult to treat, often requiring a combination of non-pharmacological and pharmacological treatment strategies. Although currently there are no specific medications licensed for the treatment of breathlessness, there is increasing evidence to suggest that morphine can be used safely to treat this distressing symptom.[10,14–17]

This discussion offers a narrative, pragmatic review of the recent evidence for using low dose, oral morphine (≤30 mg/day) in patients with COPD and refractory breathlessness, who are not in the terminal phase (last few days) of their illness. This paper will address the efficacy and safety of morphine in this patient group, and will review current guidelines regarding palliation of patients with advanced lung disease. In addition, we describe clinical recommendations based on the current evidence and the clinical experience of the authors, for practical prescribing of morphine for patients with COPD.

Measuring breathlessness prior to commencing a trial of morphine

Refractory breathlessness is common in COPD patients but remains undertreated.[8,18] As individuals systematically understate their breathlessness unless specifically asked, it is important to measure routinely and regularly dyspnoea in all COPD patients, using at least one dyspnoea scale.[19] This allows assessment of baseline severity to guide management, as well as determining the effect of treatment.[13,20,21] Assessment includes measuring both the breathlessness intensity and the distress caused to the patient. Additionally, it is useful to measure the effect of breathlessness on quality of life and exercise capacity because some patients report no improvement in breathlessness intensity and unpleasantness; nevertheless, they may report increased exercise capacity.[15] Multiple tools exist for assessing breathlessness; however, there is no consensus regarding which is the best clinical assessment tool.[20,21]

The Modified Medical Research Council breathlessness scale (MMRC) is an updated version of the original scale, (numbered 1–5), which was developed in the UK in the 1940s.[22] The MMRC scale uses a simple grading system (0–4) to quantify the disability associated with dyspnoea. It does not directly measure breathlessness intensity or unpleasantness, both of which can be measured on a visual analogue scale (VAS) (0–100 mm) or numerical rating scale (0–10). In addition to being useful for predicting survival in patients with COPD,[23,24] the MMRC scale is a useful screening tool to identify patients with refractory dyspnoea. Patients with severe COPD (forced expiratory volume in 1 s of less than 50% predicted) and an MMRC breathlessness score of 3–4, despite optimal treatment of all reversible causes of dyspnoea, may benefit from an opioid trial.[21]

Opioids

Opioids are the most studied and most commonly used medication class to treat refractory breathlessness. The exact mechanisms by which opioids alleviate breathlessness are unknown. Postulated mechanisms include altered central perception of breathlessness, reduced spontaneous respiratory drive, reduction in total ventilation, increased ventilatory efficiency with exercise, a reduction in responses to hypoxaemia and hypercapnoea, and an effect on bronchoconstriction.[25,26]

Opioid efficacy

In 2002, a systematic review and meta-analysis of nine randomised, placebo-controlled trials demonstrated that oral and parenteral opioids significantly reduced breathlessness intensity, as measured on a VAS.[17] Although there was no demonstrated increase in exercise tolerance, the doses used were low (5–40 mg oral morphine equivalent/day), with three studies administering a single opioid dose. Seven of the nine studies included only COPD patients (n = 94). Reported side-effects included drowsiness, nausea, vomiting, dizziness, constipation and opioid withdrawal syndrome. Nebulised opioids, although associated with fewer side-effects, did not significantly reduce breathlessness intensity.

Further to that review, in 2003 Abernethy *et al*. published the results of an adequately powered, randomised, double-blind, placebo-controlled, crossover trial investigating the efficacy of sustained release morphine in relieving dyspnoea in opioid naïve outpatients with breathlessness at rest despite maximal medical treatment.[10] A total of 48 participants (of whom 42 had

COPD) received 20 mg sustained release morphine daily for 4 days followed by 4 days of placebo or vice versa. Morphine improved sleep and reduced dyspnoea intensity, with a mean improvement of 9.5 mm on VAS. This result was both statistically and clinically significant.[27] There were 10 participants who withdrew from the study; five of these were due to morphine side-effects including nausea, vomiting, constipation and sedation. There were no reports of respiratory depression.

More recently, Currow *et al*. completed a phase 2 study to determine the minimum effective daily dose of morphine required to improve breathlessness, and followed up with a phase 4 study to establish whether benefits were sustained in the long term.[15] In this open-label, prospective, cohort study, 83 participants (45 with COPD) were started on 10 mg sustained release morphine daily, with weekly dose titration by 10 mg/day up to 30 mg/day in non-responders. Participants who responded to morphine and continued to use it were followed prospectively for up to 660 days. Opioids reduced baseline breathlessness by at least 10% in 62% of participants (number needed to treat = 1.6), with 70% of those participants needing a dose of only 10 mg/day. A sustained benefit for 3 months was observed in 53% of participants who responded to morphine. The level of dyspnoea reduction in this study was clinically significant and consistent with results from other studies. Over the two phases of this study, 29 participants withdrew because of side-effects including constipation, nausea, vomiting, drowsiness, confusion, hallucinations and dizziness. There were no hospital admissions due to respiratory depression or reduced conscious level. These data suggest that low dose morphine has short-term efficacy in reducing breathlessness.

Opioid safety

A major barrier to the use of opioids as first-line treatment for refractory breathlessness in COPD patients is the fear of respiratory depression and hastened death.[28–30] To date, there have been no reports of respiratory depression from low dose oral opioids for dyspnoea in the medical literature.

In the systematic review of randomised, controlled trials investigating opioids for breathlessness, three studies measured arterial blood gases.[17] All three studies included patients with severe COPD and normal baseline carbon dioxide levels (n = 40). In two studies, patients received 5–15 mg oral morphine equivalent/day, with no significant change in $PaCO_2$.[31] In another study, patients receiving 18 mg oral morphine equivalent/day had significantly higher carbon dioxide levels (mean $paCO_2$ 35.8 mmHg) compared with patients on placebo (mean $PaCO_2$ 33.2 mmHg); however, levels remained <40 mmHg and well within the normal range.[32]

Ekstrom *et al*. recently conducted a population-based, longitudinal, prospective, cohort study to evaluate the safety of benzodiazepines and opioids in patients with very severe COPD.[16] A total of 2249 patients with COPD and respiratory failure, who were starting long-term oxygen therapy in Sweden between 2005 and 2009, was included in this study. Data on all dispensed outpatient prescriptions (prescribed for any reason) were linked to hospital admission and mortality data. There was no loss to follow up. Baseline mean arterial carbon dioxide levels on air were $PaCO_2$ = 6.2 kPa (46.5 mmHg) in patients who had not used opioids prior to study commencement, and 6.4 kPa (48 mmHg) in patients who had used opioids prior to study commencement. Dispensed prescriptions of opioids were not associated with an increased hospital admission rate. Similarly, low dose opioids (≤30 mg oral morphine equivalent/day) were not associated with increased mortality; however, high dose opioids (>30 mg oral morphine equivalent/day) were. These associations were not modified by the presence of baseline hypercapnoea or being opioid naïve. These data suggest that low dose opioids may safely be used to treat patients with COPD and refractory breathlessness.

Barriers to using opioids

In addition to concerns regarding opioid safety and side-effects, many health professionals feel they have insufficient confidence, knowledge and expertise to prescribe opioids to patients with severe COPD and refractory breathlessness.[29,30] Some clinicians are uncomfortable prescribing potentially addictive medications to patients who are not in the terminal phase of their disease or are concerned that there are not clear guidelines for prescribing opioids to COPD patients with refractory breathlessness.[29,30,33]

The concern about opioid safety may also be held by some patients and their families, who may worry about addiction or a perceived association with death and dying.[33] Similarly, as opioids are commonly used to treat pain, few patients understand that opioids have a role in treating dyspnoea, and may become confused when this is suggested. In addition some COPD patients feel guilty and stigmatised by society because their disease may be self-inflicted.[34] Consequently, they may dismiss their breathlessness as being inevitable or self-induced and therefore not deserving of treatment, resulting in a reluctance to discuss the intensity or impact of their breathlessness with their doctor. These issues highlight

the need for regular, good communication with patients and families when initiating treatment for refractory breathlessness.

Which patients respond to opioids?

Accurately predicting prognosis in COPD is challenging and may contribute to the inadequate provision of palliative care to these patients.[35–37] The disease trajectory for COPD patients involves years of chronic illness with intermittent, acute exacerbations. Although each exacerbation may be life threatening, it is difficult to predict which will be fatal. Therefore, the short-term prognosis may be uncertain, even though the final outcome is clear.[38]

Similarly, it is difficult to predict which patients with COPD and refractory breathlessness will respond to morphine. Although the evidence suggests that morphine reduces dyspnoea, not all patients respond. To date, studies investigating clinical predictors of opioid responsiveness have failed to identify consistent clinical characteristics that predict a response to therapy. Allard *et al*. found that in patients with cancer, those with less breathlessness derived more benefit from opioids.[39] Meanwhile, in a larger, international, multicentre, retrospective analysis of pooled data sets of patients (n = 213) with refractory breathlessness predominantly due to either COPD or heart failure, higher baseline dyspnoea intensity scores strongly predicted an absolute and relative response to opioid ($P < 0.001$).[40] Younger age also predicted a relative response ($P = 0.025$), but functional status and cause of breathlessness did not.

While there remains uncertainty around identification of responders, a therapeutic trial of morphine is appropriate for all patients with severe COPD and refractory breathlessness, in whom all reversible causes for dyspnoea have been optimally addressed.

Clinical guidelines for treating dyspnoea

The Australian and New Zealand guidelines for the management of COPD (the COPD-X plan), as well as multiple international COPD guidelines, recommended palliative care and the short-term use of opioids for palliating breathlessness in patients with advanced disease.[1,13,20,21,41,42] However, few guidelines offer prescribing frameworks for initiating and continuing opioids in this clinical scenario. The American Thoracic Society guidelines recommend initiating 5–10 mg of oral morphine to be used three to four hourly as needed.[13] Given many clinicians are unfamiliar with prescribing and dosing opioids for refractory breathlessness, the current lack of consistent prescribing guidance is a significant barrier to using opioids to treat refractory dyspnoea.

Approaches to prescribing morphine

In our clinical experience, prescribing morphine to patients with COPD and refractory breathlessness requires sensitivity and good communication skills in order to address possible concerns raised by the patient, family or other health professionals. It may require several discussions over many months with the patient and family members, about the role of morphine (including its side-effects and community perception) to allay fears and reach the point of acceptance.

Although the current evidence supports the use of regular, low dose oral morphine, it is not known which is the best opioid or optimal prescribing regimen for patients with refractory dyspnoea. Therefore when considering initiating an opioid and different treatment regimens, it is important to consider a variety of patient factors, in addition to the patient's wishes. Many COPD patients are older, live alone, have significant co-morbidity and use multiple medications, any of which may increase the risk of toxicity or dosing error. As such prescribing should always be individualised.

In our clinical practice, we commonly initiate either immediate release oral morphine 2.5 mg, as needed four to six hourly, or sustained release morphine 10 mg once daily (the latter being the preferred option) (Table 1). The first treatment approach allows the patient, family and prescribing physician time to become familiar and confident using morphine, while also minimising side-effects. However, actual usage may be low, thus patients may prematurely stop treatment due to a perceived lack of efficacy, while using a subtherapeutic dose. The second approach is evidence based, is simpler therefore improving compliance and utilises a therapeutic dose from commencement. Additionally, the sustained release formulation provides a smoother pharmacokinetic profile over 24 h, whereas with immediate release formulations, there may be more issues with higher peak and lower trough drug concentrations.[43–45] However, not all patients will accept the second regimen immediately. As gastrointestinal side-effects are predictable and may occur immediately, we initiate prophylactic treatment for constipation on commencing morphine.

Once morphine has been started, it is important to regularly assess response (ideally measured on a VAS) and side-effects. Patients and carers should be informed on commencing morphine that it may take time to see a therapeutic effect. Thus any dose escalation should only occur at weekly intervals, to a maximum dose of

morphine 30 mg/day.[15] Dosages above this threshold may result in increased toxicity, and it is currently unclear whether higher doses improve response rates.[15,16] If patients do not report an improvement in breathlessness despite taking a therapeutic dose, then the morphine should be stopped. A repeat morphine trial in the future can be considered for these patients.

Patients and their carers need support during the process of starting morphine for refractory breathlessness, either from the prescribing physician, their general practitioner (GP) or from a specialist respiratory or palliative care nurse (Table 2). Providing written information about dosing and side-effects, and offering regular contact may improve compliance, reduce anxiety and allow for prompt treatment of side-effects. We recommend specific contact (ideally by telephone) be made with other healthcare professionals involved in the patient's care such as GP and pharmacists, who may otherwise advise patients against using morphine based upon a lack of awareness of the benefits and safety when administered appropriately.

Table 2 Practical tips for initiating morphine

	Suggestions
During the clinic visit	1. Discuss side-effects and likely duration. Always prescribe laxatives with morphine and offer an anti-emetic 2. Provide written information regarding morphine formulation to be used, dosing regimen and possible side-effects 3. If using morphine liquid, assess ability to draw up correctly the correct dose and provide with low reading syringes 4. Book follow-up visit within 2–4 weeks to assess treatment response and side-effects, and titrate dose as needed
After the clinic appointment	1. Contact general practitioner (GP) on the same day to notify that morphine (formulation and dose) has been started for refractory breathlessness 2. Telephone the patient/carer within 3 days to check understanding with dosing, assess compliance and discuss any side-effects 3. Home visit by nursing team within 7 days to review ability and understanding to administer correct dose (tablet or liquid consumption), assess compliance and any side-effects 4. Ensure ongoing access to prescribing physician, community respiratory/palliative care nursing team or GP

Integrated palliative care

Clinicians who do not feel comfortable prescribing morphine to patients with COPD and refractory breathlessness may prefer to refer these patients on to a respiratory physician with expertise in this area or to specialist palliative care. However, currently, relatively few patients with non-malignant disease are referred to specialist palliative care, and existing models of palliative care may not be well suited to the needs of patients with severe COPD.[14,46–48] Consequently, in two of our institutions, we have developed multidisciplinary clinics for patients with advanced lung disease. Our respiratory and palliative care services work in partnership, with the aim of integrating general palliative care into standard respiratory outpatient care, while improving access to specialist and community palliative care. In addition to these clinics,

Table 1 Morphine regimens to treat refractory breathlessness

	Regimen 1	Regimen 2
Starting dose	• Morphine (immediate release) liquid 2.5 mg orally 4–6 hourly as needed	• Morphine (sustained release) 10 mg once daily
Adjusting dosing	• Encourage use • Monitor response (ideally using VAS) and side-effects • Increase to morphine 5 mg orally 4–6 hourly as needed • Once stable with no dose change over 2 weeks, consider conversion to a daily, sustained release formulation • Stop treatment if no reported improvement in dyspnoea	• Monitor response (ideally using VAS) and side-effects • Increase as needed at weekly intervals by 10 mg/day to maximum dose of 30 mg once daily. • Stop treatment if no reported improvement in dyspnoea on maximum dose
Advantages	• Patient/carer is in control of dosing, so allowing time for acceptance and familiarisation with using morphine • Side-effects minimised	• Initiation dose may be therapeutic thus improving compliance • Initiation dose is relatively low, therefore usually few side-effects • Evidence-based regimen
Disadvantages	• Compliance may be poor • Patient may discontinue treatment prematurely due to perceived lack of efficacy while taking sub-therapeutic doses	• Patient/carer may be reluctant to use regular morphine if unfamiliar with or apprehensive about opioids

VAS, visual analogue scale.

respiratory nurse specialists from the hospital provide ongoing follow up over the telephone and through an outreach home-visiting service to support patients at home and work with the community palliative care team directly.

Future research

There is increasing evidence to support the short-term efficacy of oral morphine, without significant toxicity, for treating refractory dyspnoea in patients with COPD.[10,15–17,49] However, many questions remain unanswered. Currently, clinical trials using other opioids are in progress to determine whether there is a class effect and to identify which opioid is most efficacious. Further work to determine the optimal dosing regimen, long-term efficacy, clinical factors that predict opioid response, and to identify synergistic agents is needed. In addition, there is much to learn about the sensation of dyspnoea itself and how drugs act to reduce this sensation.[50]

Conclusion

Refractory breathlessness is highly prevalent and is a source of significant suffering for patients with COPD. Current evidence supports the short-term efficacy of regular, low dose oral morphine, without significant toxicity, for treating refractory breathlessness, but current guidelines offer varying advice regarding prescribing. A framework to consider, prescribe and monitor morphine therapy in the setting of refractory breathlessness offers useful practical guidelines for clinicians. A series of areas requiring further research has been identified, most particularly around the role of opioids other than morphine, the long-term efficacy, the physician perceived concerns to opioid use and more broadly the future palliative care service provision for this patient group. In the meantime, for patients with COPD suffering with refractory breathlessness, morphine appears to offer safe, effective symptom relief.

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