# Chronic refractory dyspnoea

## Evidence based management

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**Background**
Chronic refractory dyspnoea is defined as breathlessness daily for 3 months at rest or on minimal exertion where contributing causes have been treated maximally. Prevalent aetiologies include chronic obstructive pulmonary disease, heart failure, advanced cancer and interstitial lung diseases.

**Objective**
To distil from the peer reviewed literature (literature search and guidelines) evidence that can guide the safe, symptomatic management of chronic refractory dyspnoea.

**Discussion**
Dyspnoea is mostly multifactorial. Each reversible cause should be managed (Level 4 evidence). Non-pharmacological interventions include walking aids, breathing training and, in chronic obstructive pulmonary disease, pulmonary rehabilitation (Level 1 evidence). Regular, low dose, sustained release oral morphine (Level 1 evidence) titrated to effect (with regular aperients) is effective and safe. Oxygen therapy for patients who are not hypoxaemic is no more effective than medical air. If a therapeutic trial is indicated, any symptomatic benefit is likely within the first 72 hours.

**Keywords**
dyspnoea; palliative care; chronic obstructive pulmonary disease; heart failure; neoplasms; lung diseases

Dyspnoea is experienced in many chronic, progressive diseases. Underlying aetiologies include chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung diseases, neurodegenerative diseases (including late stage motor neurone disease), and any disease causing severe muscle loss from cachexia.[1–3] Major differences in dyspnoea between underlying aetiologies include the intensity of the breathlessness and the length of time the breathlessness has been present. For example, people who have COPD are likely to have had more intense breathlessness over many years.[4–6] A range of underlying aetiologies cause the similar subjective sensation of chronic dyspnoea, suggesting that there may be a common central nervous system pathway for perceiving and mediating breathlessness, irrespective of the underlying aetiology.[5,7]

The symptomatic management of chronic refractory dyspnoea (CRD) has not been part of the training of many general practitioners. As new evidence emerges to improve the symptomatic management of CRD, there is an opportunity to update practice.

## Objective

As part of a larger project in which a respiratory physician piloted academic detailing to GPs about the evaluation and treatment of CRD, evidence-based detailing material was developed from the peer-reviewed literature by the Drug and Therapeutic Information Service (DATIS). Papers were sourced from a literature search of PubMed, EMBASE, Caresearch and the Cochrane Database of Systematic Reviews and updated from recently released evidence-based guidelines (The American Thoracic Society, The American College of Physicians). The aim of this article is to present the key current clinical evidence distilled from this process.

## Recommendations

Three key recommendations for the evaluation and treatment of CRD arise from the peer-reviewed literature, followed by areas where evidence is insufficient or does not support several current clinical practices (*Table 1*).

## Address reversible contributing causes (Level 4 evidence)

Chronic refractory dyspnoea can be defined as chronic breathlessness at rest or on minimal exertion, which persists despite the maximal therapy of any underlying conditions that might

cause or worsen the symptom.[8] The first principle of management is therefore to establish that the patient's chronic dyspnoea is truly refractory. Consensus guidelines support this assessment.[9] History and examination may elicit potentially reversible causes of dyspnoea such as anaemia, a pleural effusion or anxiety, for which a specific treatment can be put in place.

Dyspnoea is mostly multifactorial, requiring the optimisation of the management of each contributing causal factor. Physical factors (such as cardiac failure, respiratory tract infection, anaemia or hypoxaemia) and psychological factors (such as anxiety) may have reversible components, although it cannot be predicted how much dyspnoea will be reduced by reversing these factors. By contrast in cachexia, dyspnoea intensity is likely to worsen in proportion to the progression of the syndrome unless the underlying pathology can be treated effectively.

Although it may seem obvious that reversible factors should be addressed, a consecutive case series of 100 people with advanced cancer who were 'currently short of breath' demonstrated that the majority had at least one factor that was potentially reversible at the time of assessment.[1] People had a median of five factors contributing to dyspnoea including: untreated bronchospasm (52%), hypoxaemia (40%), anaemia (20%, of whom 1 in 5 had a haemoglobin of <8.0 gm/L), acute or recent myocardial ischaemia (12%) or atrial fibrillation (5%). Treating any of these potentially reversible causes generates its own patient burden, such as the need for hospital admission (eg. blood transfusion) or increased monitoring (eg. use of digoxin). Such burden needs to be weighed carefully against any potential benefit. Specialist referral may be of benefit in confirming the treatment options of any potentially reversible causes that have been maximally treated.

In one study, there was poor correlation between anxiety scores and dyspnoea, and only one person had breathlessness attributed solely to anxiety.[3] Although anxiety is considered a contributing factor to CRD, it is rare for it to be the only initiating factor without other precipitants.

## Non-pharmacological interventions for the relief of breathlessness (Level 1 evidence)

By far the largest body of quality evidence for the management of chronic refractory breathlessness comes from studies of non-pharmacological interventions. The clinical measures have recently been summarised in a Cochrane review of randomised controlled trials.[10] There are high levels of evidence to support pulmonary rehabilitation in people with COPD.[11,12] There are moderate levels of evidence to support the use of

**Table 1. Key clinical messages for the evidence based evaluation and symptomatic treatment of chronic refractory dyspnoea**

| | | Intervention | Example | NHMRC level of evidence |
|---|---|---|---|---|
| **Consensus guidelines** | **Clinical evaluation** | Establish that the patient has refractory chronic dyspnoea by ensuring that the treatment of any underlying causes that may be contributing to the symptom have been optimised | • Arrhythmia management<br>• Transfusing when significant anaemia is present<br>• Optimising the treatment of COPD | Level 4 (case series)[1] |
| **Established benefit** | **Intervention** | Employ evidence based non-pharmacological interventions | • Chest wall vibration<br>• Transcutaneous electrical nerve stimulation (TENS)<br>• Walking aids<br>• Breathing techniques, including managing anxiety | Level 1 (meta-analysis)[25] |
| | | Use regular, low dose oral opioids (together with regular aperients) to reduce dyspnoea (evidence) in conjunction with non-pharmacological interventions | Sustained release morphine (Kapanol®) 10 mg mane orally regularly with docusate with senna 2 tablets mane orally | Level 1 (meta-analysis)[13,16,18] |
| | | Oxygen (rather than medical air) in those with COPD who do not qualify for long-term home oxygen | Oxygen 2 L/min using nasal cannulae | Level 1 (meta-analysis)[22] |
| **Established lack of benefit** | **Intervention** | Oxygen offers no advantage over room air for people who do not qualify for long-term home oxygen | A therapeutic trial for 72 hours may be justified: there may be individual benefit but this is not seen at a population level | Level 1 (meta-analysis)[26] |
| **Poor quality evidence** | **Intervention** | Benzodiazepines | Not applicable: there is no evidence of net benefit | Level 1 (meta-analysis)[10] |

NHMRC = National Health and Medical Research Council

walking frames (with the benefit thought to derive from improved mechanical function of the chest wall) and breathing training (including ways of managing anxiety).[10]

## Pharmacological interventions (Level 1 evidence)

Level 1 evidence from a meta-analysis of oral or parenteral opioids,[13] supported by an adequately powered, crossover, double blind, randomised controlled trial of 20 mg sustained release morphine each morning, generated an absolute reduction in breathlessness of 8 mm on a 100 mm visual analogue scale (VAS).[6] These trials have mean baseline population levels of breathlessness of approximately 50 mm, generating a relative reduction of 16–22%. Predominantly, the studies have been in people with COPD. Recently, professional bodies including the American Thoracic Society[14] and the American College of Physicians[15] have endorsed the efficacy and safety of regular, low dose opioids in the palliation of chronic refractory breathlessness. In the Australian context, prescriptions can only be written without repeats for the opioids in breathlessness, as this is not a registered indication for Authority (repeat) prescriptions.

The phase 3 studies have been complemented by a prospective phase 4 study that accumulated more than 30 patient years of data, again predominantly in people with COPD.[16] This study titrated opioids to achieve a 10% relative reduction over each individual participant's own baseline dyspnoea intensity score. Of those who derived benefit, 69% achieved this reduction with 10 mg of sustained release morphine every 24 hours and another 23% responded at 20 mg. People who had an acceptable response and continued morphine were followed prospectively for up to 660 days. No one was hospitalised for respiratory depression or obtundation, supporting data that opioids in steady state at low doses have no effect on partial pressure of carbon dioxide ($PaCO_2$) or oxygen saturation ($SpO_2$) in this patient group.[17] This is in contrast to the use of bolus intravenous doses of morphine used postoperatively or after trauma, where acute toxicity occurs.[18] Even at very low doses, constipation needed to be managed actively. There was no evidence of tachyphylaxis.

Morphine is contraindicated in very severe renal failure due to the potential accumulation of renally excreted active metabolites. Currently, there is no strong evidence for the use of opioids other than morphine, although clinical trials are in progress.

## What is a clinically significant improvement in patients with chronic refractory dyspnoea?

An improvement as low as 5.5 mm on a 100 mm VAS will be discerned by patients with CRD as being a meaningful improvement. By contrast, in acute dyspnoea, the difference needs to be about 20 mm for a clinically meaningful reduction.[19–21] The improvements relate only to dyspnoea intensity, with data on the unpleasantness of dyspnoea, quality of life and functional improvements still awaited.

## Which therapies are identified for specific underlying aetiologies?

A meta-analysis of people with COPD who did not qualify for long-term home oxygen suggested for the first time that dyspnoea intensity may be improved more with oxygen than medical air.[22]

## Which therapies do not have evidence to support them?

Oxygen therapy is widely used for dyspnoea, often with little or no reference to the person's partial pressure of oxygen or pulse oximetry. Level 1 evidence suggests that there is no symptomatic advantage of oxygen over medical air in people with cancer who do not qualify for long-term home oxygen.[23] (Oxygen is easier to supply than medical air and therefore widely used.) Any benefit generated is likely to be achieved in the first 72 hours, so an individualised trial is a reasonable approach. Subgroup data are not available for underlying aetiologies other than cancer and COPD.

The anxiolytic, buspirone, was recently studied in a large randomised controlled trial (n=433).[24] This study did not show benefit over placebo at 4 weeks in people with chronic refractory breathlessness. This raises questions as to how significant the role of anxiety is in the genesis or maintenance of CRD.

## Which therapies have an inadequate evidence base?

Benzodiazepines are widely used for dyspnoea given their anxiolytic effects in the short-term. A recent systematic review did not find sufficient evidence to support the benefit of benzodiazepines in reducing the symptom burden of CRD, although the studies done to date have been underpowered.[25] An adequately powered study is needed with toxicity and benefit measured longitudinally.

## Summary

Chronic refractory breathlessness can be managed by:

- treating reversible causes
- considering non-pharmacological treatments
- titratrating regular oral sustained release morphine, starting with low doses (together with regular aperients).

This approach provides an opportunity safely to reduce the intensity of dyspnoea in patients.


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Competing interests: Amy Abernethy has received payment from Novartis and Pfizer for consultancy and is a board member of Advoset and Orange Leaf Associates.

Provenance and peer review: Not commissioned; externally peer reviewed.

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