

MANAGEMENT OF REFRACTORY DYSPNOEA: EVIDENCE-BASED INTERVENTIONS

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Abstract

Breathlessness is a common and distressing symptom in both malignant and non-malignant conditions. Both pharmacological and non-pharmacological strategies are necessary to minimise symptom burden and distress. Assessing the individual's needs and clarifying the goals of treatment is an important first step in determining an effective treatment plan. Although the evidence supporting the use of some of these therapies is variable, there is an increasing evidence base to inform clinical decision making and treatment plans. Pharmacotherapy with opioids is a common and effective strategy for managing breathlessness, yet requires judicious titration and management. The adverse effects of opioid therapy, including constipation and drowsiness, can be anticipated and managed with adjunctive therapies. The use of oxygen in people who are hypoxaemic is supported, but is of limited value in people who are not hypoxaemic. Individualised strategies and advance care planning is important to avoid unnecessary hospitalisations and futile treatments at the end of life. There is a clear mismatch between the prevalence and burden of this problem and data to inform evidence-based guidelines. Refractory breathlessness is a fertile area for ongoing research and requires increased attention to address the burden of this highly prevalent symptom.

Breathlessness is a common and distressing symptom for patients and carers, occurring in 50-90% of individuals in both malignant and non-malignant conditions.¹ In palliative care, the intensity of breathlessness frequently worsens as death is imminent.² In spite of the prevalence of this symptom, patho-physiological processes remain poorly understood and the sensation is highly subjective, challenging development of evidence-based approaches.³ Available data suggest that there is more than one mechanism involved in the pathogenesis and manifestation of breathlessness.⁴

An important consideration for health professionals is that in the real world of clinical practice, it is rare for an individual to have a single condition responsible for inducing the sensation of breathlessness. Breathlessness may be related to a prior condition, disease progression or it may be iatrogenic. In addition to causes of refractory breathlessness, commonly chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) are comorbid conditions of individuals with cancer.⁵⁻⁷ Furthermore, breathlessness can also be associated with deconditioning associated with advanced illness.^{8,9} This means that the diagnosis, management and treatment of dyspnoea is complex and multifaceted and requires an appreciation of the biological, psychological and social impacts of breathlessness. Importantly, this requires appraisal of the individual's needs and establishing the goals of therapy.¹⁰

Much of the data derived for recommendations relating to management of refractory breathlessness in cancer

is derived from non-malignant populations.¹¹ However, when disease is advanced and there is a need to focus on symptom management, these data provide an important foundation for empirical treatment. The heterogeneity of both patient populations and the symptom challenge evidence-based guidelines. In spite of these challenges, it is important that the clinician takes a systematic approach to the diagnosis and management of this symptom.

Assessment and planning: foundation of effective treatment

In order to develop an effective treatment plan it is important to identify the cause, where possible, and identify reversible causes such as pleural effusions, heart failure exacerbations or anaemia. Implementing strategies for monitoring the severity of breathlessness across the illness trajectory can assist in monitoring and managing exacerbations.¹ Implementing a valid and reliable strategy for assessing breathlessness, such as a Visual Analogue Scale, Numerical Rating Scale or modified Borg Scale, can assist in monitoring and evaluating symptomatic treatment.^{12,13} Although there can be challenges in administering these instruments, implementing a measure routinely in clinical practice can assist in treatment and management. Although self-report is optimal, objective assessment using tools such as the Respiratory Distress Observation Scale may be useful.¹⁴ Calls for consensus of the choice of instruments for dyspnoea trials is an important consideration, particularly in the palliative care population.¹⁵

Unfortunately, once breathlessness is refractory, many non-pharmacological interventions have been trialled and reversible causes assessed. As both malignant and non-malignant diseases progress, pharmacotherapy is an essential part of treatment integrated within a supportive care plan, recognising the physical, social, psychological and spiritual needs of patients and their families. As breathlessness is a common cause for hospitalisation, pre-empting hospital presentations with action plans in the event of sudden worsening of breathlessness is contingent upon effective palliative strategies. Evidence-based recommendations are limited by the current data available to inform decisions, underscoring the importance of ongoing research. Although there is increasing and emerging data in managing breathlessness,¹⁶ we are still limited by the absence of adequately powered clinical trials to definitively define treatment for many of the options currently used.^{1,17}

Opioids

Although the mechanisms of action remain unclear, opioids are a frequently used and effective strategy for managing refractory breathlessness.^{17,18} Apart from morphine, which can be administered in immediate or sustained release oral preparations, subcutaneously or intravenously, other preparations include dihydrocodeine, hydromorphone and fentanyl. Opioids cause vasodilation and decrease the chemoreceptor response to hypercapnia and hypoxia. These responses may decrease the sensation of breathlessness through reducing preload and pulmonary congestion. The effect of opioids through decreasing anxiety and the subjective sensation of breathlessness, contributes to decreasing the respiratory rate and oxygen consumption.

Encouraging results have been found in the use of opioids in both malignant and non-malignant populations for relieving dyspnoea.^{17,19,20} Stigma and scepticism regarding opioids are important factors in the low uptake of opioid therapy.²¹ The commonly cited reasons for avoiding opioids, such as causing respiratory depression and reducing life expectancy, are not substantiated by available data when used chronologically in low doses. Minimising physical and psychological distress is not associated with shortening life expectancy. The optimal type, dose and mode of administration remain less clear and are the focus of ongoing research. Growing clinical experience indicates that judicious titration of dosage and anticipation of adverse effects, such as constipation, improves compliance with opiates. Adverse effects of opioids such as sleepiness or nausea are infrequent, and can be overcome by dose titration. Each patient should be assessed individually and appropriate dose adjustments made based on the patient's current medical condition. Starting with a low dose and up titrating slowly can allow the monitoring of adverse events and the tailoring of dosage. Constipation does not readily respond to dose titration and requires proactive

bowel management and adjunctive administration of regular laxatives. For clinicians less experienced in opioid therapy prescription and management, enlisting the support of a more experienced colleague for mentorship and a pharmacist to assist with dosing is an important consideration.²² Although conceptually alluring, the use of nebulised opioids in the treatment of dyspnoea is not supported by individual studies nor a meta analysis.¹⁸

Diverse pharmacological agents

Corticosteroids can be effective in the treatment of dyspnoea related to carcinomatous lymphangitis, superior vena cava syndrome, tracheal obstruction and bronchospasm associated with COPD and asthma.²³

Bronchodilators are used in the management of bronchospasm and may provide relief of breathlessness caused by airflow obstruction through relaxing the muscles around airways and increasing muscle tone.²⁰ Common bronchodilators include the short acting agents albuterol sulfate, levalbuterol and pirbuterol acetate, and the long-acting agents ipratropium bromide, salmeterol xinafoate, formoterol, tiotropium and terbutaline sulfate. Metered dose inhalers should be used with a spacer to improve the patient's ability to receive the full dose. Proper dosing is often dependent on perfecting the technique of these technically challenging devices. Failure to achieve therapeutic doses due to poor usage of the delivery system is not uncommon. Considering administration by a nebuliser may be a more reliable alternative, particularly if the patient is highly symptomatic.

Diuretics may be useful in the treatment of breathlessness caused by oedema. Generally loop diuretics, such as frusemide, are prescribed. Standard dosing for frusemide is 20-40mg orally, subcutaneously or intravenously once or twice a day. In individuals where heart failure is advanced or diuretics have been administered over a long period of time, diuretic resistance may be a problem requiring tailoring of the timing of dosage and the addition of a thiazide diuretic.²⁴ Diuretics must be used cautiously given the potential for hypovolemia and electrolyte disturbances, particularly hypokalaemia. Consideration of electrolyte substitution, particularly potassium and magnesium should be considered.²⁴ Importantly, if the patient is incontinent, strategies to maintain patient comfort, dignity and preserve skin function should be implemented.

A recent meta-analysis conducted by Simon and colleagues did not show a beneficial effect of benzodiazepines for the relief of breathlessness in patients with advanced cancer and chronic obstructive pulmonary disease. These authors concluded that there was a small, non-significant trend towards a beneficial effect. Benzodiazepines caused more drowsiness compared to placebo, but less compared to morphine. They recommend considering benzodiazepines when opioids and non-pharmacological measures have failed to control breathlessness.²⁵ The decision to

prescribe these agents should be based on the presence of anxiety impacting on the sensation of breathlessness.¹⁰ Benzodiazepines reduce the sensation of breathlessness through decreasing the anxiety associated with breathlessness. As benzodiazepines are metabolised in the liver to long-acting metabolites, short-acting drugs such as lorazepam are preferred, especially in the elderly or in patients with impaired liver function. Midazolam, when administered either subcutaneously or intravenously as an addition to an opioid, has been shown to reduce the terminal agitation and anxiety that may be associated with dyspnoea.

There is some data to suggest that phenothiazines can be beneficial in the treatment of breathlessness.²⁶ In addition to reducing anxiety, phenothiazines possess anticholinergic properties that can be useful in managing increased respiratory secretions or in controlling nausea. Chlorpromazine has been found to be effective for the relief of dyspnoea in advanced cancer patients and also relieves terminal restlessness.²⁷ Side-effects of phenothiazines may include hypotension and extrapyramidal effects, which may limit tolerability of these agents.

Agents such as aminophylline and theophylline have been found to dilate the bronchi and improve diaphragmatic contractility in individuals with COPD, irrespective of any bronchoconstriction. There have also been reports of use in the palliative care setting.²⁸ Theophylline can also be useful in managing dyspnoea when combined with albuterol and ipratropium. Adverse effects include vomiting, hypokalaemia, hyperglycemia, tachycardia, cardiac dysrhythmias, neuromuscular irritability and seizures. Given the narrow therapeutic index, frequency of side-effects and the lack of evidence for efficacy, these agents are often not well tolerated in patients with advanced illness and their use should be reserved for people already established on these therapies.

Nebulised frusemide has been identified as a novel approach to dyspnoea management. The precise mode of action is unclear and it is thought to have multiple pathways of action. Potential modes of action are on the pulmonary stretch receptors and vasculature. A recent review has shown that this agent had a positive influence on dyspnoea and physiological measurements. However, the authors provide the caveat that findings are mixed and data to date comes from small trials and observational studies.²⁹ Further investigation into the mechanistic and therapeutic actions of nebulised frusemide is warranted.

Oxygen therapy

Oxygen therapy continues to be very controversial in the management of dyspnoea, as there is little data supporting its use in the nonhypoxic patient,³⁰ although the role in people who transiently desaturate, particularly on exertion or overnight, can be made more easily. In patients who are hypoxic on room air, the benefit of supplemental oxygen is most

likely related to flow of gas over the face. Currently, guidelines only recommend oxygen for dyspnoeic patients, with hypoxaemia of less than PaO₂ of 55-60mm Hg. A recently published systematic review of short-term oxygen in people with cancer who did not qualify for domiciliary oxygen, showed no symptomatic benefit.³¹ A recent international, multicentre, randomised comparator control study assessed long-term oxygen (≥15 hours/day) therapy versus air in a palliative care population, who had intractable dyspnoea at rest and on minimal exertion and did not qualify for home oxygen (NHMRC 375127/NIH R01 AG026469-01). It showed that both oxygen and air delivered symptomatic benefit when used at two litres per minute via nasal prongs for more than 15 hours a day.³²

Non-pharmacological therapies

Both invasive and non-invasive ventilation can be considered for progressive illnesses when the symptom is refractory to other therapies.³³ However, the purpose and goals of treatment need to be carefully considered.³⁴ There is an increasing concern of the futility of some decisions to provide mechanical ventilation.³⁵ Escalation of symptom burden avoiding such scenarios can be achieved by careful planning and the institution of an action plan,³⁶ providing strategies for self-management and instructions to health professionals where there is a deterioration in status about the person's wishes. In life limiting illness, advance care planning is important to document the patient's wishes and outline a clear plan for care.³⁷

There is a wide array of non-pharmacological therapies to manage dyspnoea, by either changing physiologic factors or modifying the subsequent emotional response associated with the sensation of breathlessness, as shown in table 1. Current research has been geared primarily toward patients with COPD, however the utility of this modality for both malignant and non-malignant disease is increasingly evident. Increasingly in cancer, there is an interest in rehabilitation programs similar to those seen in cardiac and respiratory rehabilitation.^{38,39} The aims of structured rehabilitation programs are to facilitate the coordination of care, provide information and facilitate access to resources, optimise physical and social function and provide psychosocial and peer support.

The purpose of rehabilitation for patients with cancer is similar to that for patients with other diseases. The anticipated progression of disease, and any associated treatments must be considered carefully when goals are formed. When tumour progression and treatment causes a functional decline, or when the disease causes a fluctuation in abilities, rehabilitation assumes a supportive role of seeking to minimise the rate of decline, and goals should be adjusted to meet the needs of the patient and their families. The strong evidence for appropriate exercise in decreasing the symptom burden of dyspnoea and the increased adherence obtained from group settings is an important consideration.^{40,41}

Table 1: *Nonpharmacologic therapies for dyspnoea*

- Reassurance and strategies to minimise the anxiety/dyspnoea cycle.
- General supportive measures such as optimising nutritional status.
- Positioning to support ventilation – sitting up or leaning forward.
- Muscle strengthening through exercise and respiratory muscle training.
- Energy conservation techniques to minimise exertion and optimise activities of daily living.
- Relaxation through techniques such as guided imagery and progressive muscle relaxation.
- Breathing training through pursed lips and diaphragmatic breathing.
- Counselling techniques such as mindfulness therapy.
- Cool air and moving air across the face through use of a fan or gas administration via nasal cannula or mask.
- Non-invasive ventilation.
- Acupuncture/acupressure.
- Massage to promote relaxation and posture.

The use of complementary and alternative treatments, such as massage, to decrease anxiety is increasing. Emotional responses to illness, such as anxiety and anger, can precipitate and worsen breathlessness.⁴² Although some studies have assessed these therapies, the widespread recommendation is limited due to methodological factors such as small sample sizes.¹³ Relaxation and biofeedback techniques have demonstrated some efficacy in breathlessness in COPD and in patients with CHF. A critical strategy is addressing anxiety before it escalates into a situation of panic.⁴³ Distraction is a useful technique and the playing of music and getting the patient to watch a movie can be useful. Breathing exercises and meditation strategies such as Buteyko and Pranyama, that use diaphragmatic breathing, can relieve the sensation of dyspnoea and promote a sense of control, however require a motivated and cognitively intact person.^{44,45} Bernardi and colleagues demonstrated in a small study that training using the Ave Maria (in Latin), or a yoga mantra, improved psychological responses and increased baroreflex sensitivity.⁴⁶ For these strategies to be effective, it is important to introduce these early in the illness, as when patients become highly symptomatic or drowsy, it is difficult to teach these techniques.

Some studies have suggested there is a benefit from acupuncture.^{47,48} Strategies that promote a sense of control are likely to improve the patient's sense of wellbeing and minimise feelings of hopelessness. A recent trial of mindfulness therapy has shown

benefits in relieving dyspnoea.⁴⁹ It is important that patients and their families feel comfortable discussing alternative approaches and disclosing treatments they are undertaking.⁵⁰ The potential for deleterious drug interactions with herbs and vitamins increases as metabolic derangements occur in the advanced stages of disease at the end of life.

An important strategy in managing refractory breathlessness and maximising quality of life are energy conservation techniques.⁵¹ As symptoms worsen, activities of daily living become increasingly difficult. Implementing strategies and devices, such as walkers, to reduce energy expenditure can be useful.⁵² Involving allied health professionals, particularly occupational therapists, can contribute effectively to the dyspnoea management plan.

Palliative care

When increasing disability is evident and advanced disease processes are present, interventions and goals that focus on minimising or eliminating complications and providing comfort and support are important. Psychological and social support for the patient and family members are integral. Although a palliative approach can be provided by a range of health care professionals, particularly general practitioners, when breathlessness is refractory and front line treatments have been trialled unsuccessfully, specialist palliative care services should be accessed. It is not uncommon for existential distress to exacerbate symptoms, particularly dyspnoea.

Conclusion

Dyspnoea is a difficult and challenging symptom to manage for patients, their families and clinicians. Management of refractory breathlessness in patients with advanced disease remains challenging and further research is required to develop evidence-based strategies. Although there is a growing evidence base for interventions to manage dyspnoea, issues in clinical trial design challenge translation to evidence-based guidelines. Adequately powered, well controlled clinical trials are urgently needed to address the burden of this distressing symptom. A salient consideration in contemplating evidence-based interventions is that dyspnoea is a highly individualised and subjective symptom. As a consequence, the optimal treatment of dyspnoea will involve appraisal of the pathophysiological basis of the symptom, weighing of the potential risks and benefits of treatment and overall prognosis. Implicitly, this will entail an understanding of psychosocial, spiritual, and existential needs of the patient and their family.

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