Yorkshire Palliative Medicine Clinical Guidelines Group

Clinical guidelines for the management of terminal dyspnoea

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Objective: To review the current evidence and make recommendations for the management of terminal dyspnoea.

Introduction
Terminal dyspnoea is the subjective sensation of difficulty in breathing, occurring usually at rest, in the terminal phase of a life limiting illness. Although it is a subjective sensation, the effect of dyspnoea may manifest as physical, psychological, social and functional problems. The prevalence of terminal dyspnoea has been difficult to assess, but studies have suggested it is a common problem occurring in 29 – 74% of patients. There are many causes of dyspnoea and they can be classified according to anatomical site i.e. pulmonary causes, cardiac causes, neuromuscular causes and psychological causes. These guidelines have been developed to aid the management of patients with irreversible terminal dyspnoea due to malignant disease, chronic respiratory disease, chronic heart failure or neurological disorders.

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Competing interests: None declared

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Management options discussed in these guidelines:

1. Opioids
2. Benzodiazepines
3. Oxygen
4. Steroids
5. Nebulised drugs
6. Behavioural measures
7. Acupuncture
8. Non-invasive ventilation
9. Antisecretory drugs
1. Opioids

Evidence

A Cochrane review of opioids for the palliation of breathlessness in terminal illness was published in 2002. This included randomised double-blind controlled trials comparing use of any opioid drug against placebo for relief of breathlessness, up to May 1999. 18 studies met the selection criteria; 14 were patients with COPD, 2 were cancer patients, 1 cardiac failure and 1 interstitial lung disease. The drugs were nebulised morphine (9 studies), oral dihydrocodeine (4 studies), oral diamorphine (2 studies), immediate release morphine (1), and sustained release morphine (1), intravenous morphine (1 study). Meta-analysis of results showed a strong effect of treatment for breathlessness, which on meta-regression comparing non-nebulised and nebulised studies showed a significantly stronger effect in non-nebulised studies. An effect was indicated in exercise tolerance, but statistical significance not achieved. 11 of the studies provided information on blood gases or oxygen saturation; only 1 study showed significant increase in arterial pCO2 on dihydrocodeine, but never >40mg Hg, and oxygen partial pressure did not fall significantly. The review concluded there was evidence in favour of continuing to use oral or parenteral opioids to palliate breathlessness. Further more recent studies have supported the use of morphine for breathlessness, without compromising respiratory function: A placebo controlled study of subcutaneous morphine in 9 elderly patients with advanced cancer, and a placebo-controlled crossover study with oral morphine 2.5 or 5mg qds in patients with NYHA III/IV Chronic Heart Failure. Side effects are as expected from opioid use, but sedation and/or dizziness can be significant. There is no evidence that using immediate release morphine is better than sustained release morphine.

Summary

There is good evidence to support the use of opioids in treating breathlessness. However patients should be advised about side-effects and carefully monitored. Larger studies are indicated to establish which patients are most likely to benefit and optimal dosage regimens.

Suggested drugs and doses:

- Immediate release morphine starting at 2.5mg 4 hourly.
- Sustained release morphine starting at 10mg bd
- Subcutaneous diamorphine 2.5mg 4 hourly or 5-10mg in 24 hours.
- 4 hourly equivalent of regular opioid as breakthrough and assess response, or increase in regular opioid by 1/3.
2. Benzodiazepines

**Evidence**

There are no studies published looking at the use of benzodiazepines in the management of terminal dyspnoea in cancer patients. Trials in COPD patients have not shown any benefit and some have suggested that benzodiazepines may be harmful in patients with type II respiratory failure, but these trials used large doses of benzodiazepines, for example 40mg of diazepam. One case report found alprazolam of benefit in a patient with COPD. There is, however, a wealth of clinical experience in which benzodiazepines have been found to be helpful in managing terminal dyspnoea and they have a well established role in the management of anxiety.

**Summary**

There is a lack of published evidence to support their use, but there is a lot of clinical experience to support their use. They should however be used with caution in patients with type II respiratory failure.

**Suggested drugs and doses:**

- **Lorazepam**
  
  Half life 12 hours  
  Peak plasma level 2 hours  
  No major active metabolites  
  Dose range of 0.5mg to 4mg a day in divided doses  

- **Diazepam**
  
  Half life 20-50 hours  
  Active metabolites produced including oxazepam  
  Renal excretion  
  Dose range of 2mg to 30mg a day in divided doses  

- **Midazolam**
  
  Half life 2 hours  
  Hepatic extraction  
  Amnesic effect  
  Dose range of 10mg to 240mg per day via continuous subcutaneous infusion  
  Stat doses of 2.5mg to 10mg
3. Oxygen

Evidence

Equivocal evidence to support the use of oxygen for treating breathlessness at rest in COPD patients.

Trials assessing the use of oxygen for treating breathlessness during exercise in COPD patients found patients receiving oxygen were less dyspnoeic than those receiving air. However, the evidence that oxygen speeds recovery from exercise was equivocal.

The use of oxygen in patients with chronic heart failure has shown to be of some benefit in individual patients only.

Summary

For individual patients it may be useful to trial oxygen at rest and on exercise and assess its effectiveness. In addition to the patient’s subjective assessment of benefit, it may be helpful to monitor pulse oximetry.

Suggested drugs and doses:

- Oxygen 24% or 28% for patients with chronic obstructive pulmonary disease
- Oxygen from 24% up to 60% for all other patients

4. Steroids

Evidence

There is some clinical evidence to support the use of steroids in specific conditions, for example, lymphangitis carcinomatosis, superior vena cava obstruction or tracheal obstruction.

There is no evidence to support the use of steroids in non-specific dyspnoea.

Summary

Steroids should be considered in patients with lymphangitis carcinomatosis, SVCO or tracheal obstruction in conjunction with definitive treatment where possible. Current practice is to use high dose steroids and aim to reduce to lowest effective dose as soon as possible, and to aim for short-term use only.

Suggested drugs and doses:

- Dexamethasone, usual range 8mg to 16mg once daily
5. Nebulised drugs

A) Opioids

Evidence

8 randomised controlled trials in COPD patients and 1 RCT in cancer patients showed that there was no benefit in using nebulised opioids for shortness of breath or to increase exercise tolerance.

Summary

No evidence to support the use of nebulised opioids.

B) Saline

Evidence

One study in patients with bronchiectasis showed better sputum clearance.

Summary

Nebulised saline may be of benefit in patients who have difficulty expectorating sputum.

Suggested drugs and doses:

Normal saline 5 – 10 ml nebulised as required

C) Lignocaine

Evidence

One pilot study comparing lignocaine and saline in cancer patients showed that the effort of breathing was the same in both groups but the distress was higher in the lignocaine group.

Summary

Nebulised lignocaine may worsen symptoms of dyspnoea in cancer patients.

6. Behavioural measures

Evidence

There is good evidence demonstrating the effectiveness of pulmonary rehabilitation in COPD patients and it has been shown to improve quality of life. Use of pursed lip breathing has been shown to reduce respiratory rate and dyspnoea in COPD patients. There is equivocal evidence to support the use of relaxation techniques in COPD patients but it is widely accepted as a valuable technique.
Nursing interventions have been shown to improve dyspnoea, distress and functional capacity in a pilot study of lung cancer patients and in a large multi-centre study of lung cancer patients.

A draft of cool air across the face, usually by using a fan, has been shown to be of benefit.

The involvement of a physiotherapist and occupational therapist would be particularly useful for:

- Helping clear bronchial secretions
- Good positioning to improve respiratory mechanics
- Breathing exercises and breathing re-training
- Activity pacing and goal setting
- Addressing environmental factors
- Anxiety management
- Relaxation and distraction exercises

Summary

The use of pulmonary rehabilitation should be considered in selected COPD patients. Pursed lip breathing may be useful in COPD patients. Simple relaxation techniques and the use of a fan may provide relief in breathless patients. Nursing, physiotherapy and occupational therapy interventions may also be of benefit.

7. Acupuncture

Evidence

Level II: A trial of genuine versus placebo acupuncture in 26 patients with COPD showed subjective improvement but no change in objective measures.

Level V: A trial of 20 patients with cancer related dyspnoea showed symptomatic improvement for 24 hours in 14 patients but no change in objective measures. However, it was noted that patients had a nurse present for 90 minutes post-treatment.

Summary

Acupuncture is currently not used clinically but may be worth considering in selected patients, but note that the trials have used intensive treatment i.e. 2-3 treatments per week.

8. Non-invasive ventilation

Evidence

Non-invasive ventilation has been shown to be of proven benefit in treating type II respiratory failure due to neuromuscular disease in selected patients, and there is some evidence to suggest that it improves symptoms in patients with Motor Neurone Disease.
**Summary**

Non-invasive ventilation should be considered in selected patients with type II respiratory failure due to either COPD or neuromuscular disease. In current practice NIPPV is prescribed by a specialist respiratory physician but can be managed in the hospice setting. Careful consideration is needed regarding withdrawing treatment, which can either be gradually weaned or stopped abruptly.

**9. Antisecretory drugs**

**Evidence**

Clinical studies have not demonstrated any significant differences in the effectiveness of hyoscine hydrobromide, hyoscine butylbromide or glycopyrronium in treating death rattle. However, volunteer studies have shown that glycopyrronium has a longer duration of action than hyoscine hydrobromide or butylbromide and that all three drugs have a similar onset of action. Glycopyrronium has also been shown to have less cardiotoxicity. Hyoscine hydrobromide crosses the blood-brain barrier and may therefore cause sedation, confusion and agitation.

**Summary**

Antisecretory drugs are helpful in alleviating death rattle.

**Suggested drugs and doses:**

- Glycopyrronium 1.2–2mg via continuous subcutaneous infusion over 24 hours (stat dose of 400microg)
- Hyoscine butylbromide 60-120mg via continuous subcutaneous infusion over 24 hours (stat dose of 20mg)
- Hyoscine hydrobromide 1.2-2.4mg via continuous subcutaneous infusion over 24 hours (stat dose of 400microg)
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**Steroids**


**Nebulised Drugs**


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**Behavioural measures**


**Acupuncture**


**Non-invasive Ventilation**


**Antisecretory drugs**