Yorkshire Palliative Medicine Clinical Guidelines Group

Guidelines for pharmacological treatment of breathlessness in terminal illness

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Objective: To review the current evidence and make recommendations for the pharmacological management of breathlessness in terminal illness.

Search strategy: Evidence was examined and summarised from systematic reviews, meta-analyses and national guidelines and Medline/Embase databases were searched if the above provided insufficient information. A hierarchy of information sources was agreed within the group:

1. Cochrane/ Database of Abstracts of Reviews of Effectiveness (DARE)
2. SIGN/NICE
3. Clinical Knowledge Summaries (CKS)
4. Bandolier
5. Palliative Care Formulary, third edition
6. Medline/Embase via Search 2.0: search drug & adverse effect (with thesaurus mapping)

Searches were limited to papers published in English. See appendix 1 for the Cochrane/Medline/Embase search strategy

Level of evidence: Evidence regarding medications included in this review has been graded according to criteria described by Keeley1 on behalf of the SIGN research group (see appendix 2).

Guidelines produced: October 2010

Review date: October 2013

Competing interests: None declared

Disclaimer: These guidelines are the property of the Yorkshire Palliative Medicine Clinical Guidelines Group and are intended for qualified, specialist palliative medicine professionals as an information resource. They should be used in the clinical context of each individual patient’s needs and reference to appropriate prescribing texts / literature should also be made. The Clinical Guidelines Group takes no responsibility for any consequences of any actions taken as a result of using these guidelines.

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1) Introduction

Breathlessness is the subjective sensation of difficulty in breathing. Although it is a subjective sensation, the effect of dyspnoea may manifest as physical, psychological, social and functional problems. Breathlessness on exertion is normal with deconditioning and increasing age, but can become pathological when it interferes with normal life and functioning, or when it occurs at rest.

Breathlessness is one of the most common symptoms in the last year of life. In advanced diseases it is highly prevalent – in chronic obstructive pulmonary disease (90-95%), chronic heart failure (60-88%), cancer (10-70%). These conditions have a direct impact on the cardiorespiratory system. However, terminal illness of malignant or non-malignant aetiology of any site could cause breathlessness due to cachexia and general muscle fatigue. Prevalence of breathlessness in the terminal stages of AIDS and renal disease is 10-60%.

Pathophysiology of breathlessness

Several theories exist as to the pathophysiology of breathlessness in terminal illness. Pharmacological, and non-pharmacological, treatments are thought to act at different receptors within these pathways. Central to these pathways is the respiratory centre, located within the brain stem. The respiratory centre is modulated by information it receives via neurotransmitters and neuromodulators from higher centres within the cortex, chemoreceptors, the airways and respiratory muscles. In simplistic terms, the respiratory centre balances the ventilatory drive (demand), against the ventilatory capacity (supply), from the information it receives. If there is a shortfall in supply compared to demand, this will result in the sensation of breathlessness. Examples of such mismatch include:

- Increased ventilatory drive – e.g. muscle fatigue, exercise, panic
- Reduced ventilatory capacity – e.g. lung tumour, airway obstruction, pulmonary oedema, infection, lung fibrosis, neuromuscular diseases

Management of intractable dyspnoea aims to alter or interfere with the neuromodulatory pathways that input information to the respiratory centre, with the goal of reducing or abolishing this mismatch.

Principles of management

There are many causes of dyspnoea, and it is important to identify and treat potentially reversible causes, if appropriate. Such examples would be the treatment of a chest infection, blood transfusion for anaemia, bronchodilator therapy for acute bronchoconstriction, etc. The review of the patient by a specialist physician may be advised to ensure disease-specific treatment has been optimised, such as with heart failure or COPD.

In many cases 'targeted' treatment of the breathlessness isn't possible as there is either no effective treatment, no specific treatable cause or effective treatment is too invasive and considered to be inappropriate in the terminal stages of illness. In these situations, the breathlessness would be considered as intractable. This guideline covers pharmacological management of intractable dyspnoea due to terminal illness of malignant and non-malignant aetiology. Non-pharmacological measures are covered by a recent Cochrane review and should be considered first or in conjunction with medical management.

The terms dypsnoea and breathlessness are used interchangeably in this guideline.
2) Drugs included in the search:

The following drugs have been reviewed for the purposes of this guideline:

1. Opioids
   *Morphine
   *Fentanyl & alfentanil
   *Hydromorphone
   *Codeine & dihydrocodeine
   Oxycodone
   Buprenorphine
   Methadone
   Tramadol
   Pethidine

2. Benzodiazepines
   *Diazepam
   *Midazolam
   Lorazepam
   (Alprazolam & clorazepate included in the Cochrane review. These drugs were not searched for outwith this).

3. *Oxygen/ Heliox

4. Steroids
   *Prednisolone
   *Dexamethasone

5. *Nabilone

6. Other nebulised drugs
   *Lidocaine (Lignocaine)
   *Furosemide (Frusemide)
   *Saline

A literature search was performed on all the above drugs. The use of * denotes that some evidence (of any level) was available for review. This evidence has been discussed within the following guideline.

A summary of evidence for each drug has been presented in text form as well as summary tables for easy reference, which include the level of evidence.
Section 3: Available evidence for individual drugs

Opioids

The Cochrane review of 2001\(^5\) concludes that there is evidence to support the use of oral or parenteral opioids to palliate breathlessness although numbers of patients involved in the studies were small. The best evidence is for morphine, codeine and dihydrocodeine. No studies have compared different types of opioids in a head to head trial.

As well as reviewing these papers, we have identified papers published after the Cochrane review and have summarised findings for individual drugs below. Full details of individual studies are included in summary tables at the end of the main text. The following studies were conducted in a variety of patient groups including cancer, COPD, MND, heart failure, and lung fibrosis and opioids were found to be safe in all groups studied, at the doses used.

1) Morphine – There are a small number of small RCTs\(^{6-10}\) that support the use of non-nebulised morphine to improve dyspnoea scores.

2) Fentanyl – There is some low level evidence\(^{11-15}\) that fentanyl via a variety of routes (intra-nasal, transmucosal and nebulised) may improve dyspnoea scores. Unfortunately the only randomised study\(^{16}\) failed to recruit.

3) Codeine & dihydrocodeine – There is mixed evidence from small randomized controlled trials\(^{17-20}\) that codeine and dihydrocodeine may improve dyspnoea scores and exercise tolerance in patients with COPD and CCF.

4) Hydromorphone – A small poorly conducted non-randomised trial\(^{21}\) showed a small improvement in dyspnoea scores with hydromorphone, but this is not supported by the 1 small RCT\(^{22}\) in this area. This compared nebulised hydromorphone vs systemic hydromorphone vs placebo. Dyspnoea scores improved in all arms of the study when compared with baseline, but no statistical difference was found between the groups. There have been 3 further studies\(^{23-25}\) looking at either hydromorphone or morphine for breathlessness, which were positive for ‘opioids’, but the results do not differentiate between the 2 drugs.

5) Nebulised opioids – Since the Cochrane review (2001)\(^5\) which showed no evidence of benefit, 3 further randomised studies\(^{26-28}\) have been published which again show no further evidence. There is currently no evidence based role for nebulised opioids.

Clinical advice for opioids:

- First line opioid treatment for breathlessness would usually be morphine unless there are contra-indications. A typical starting dose in an opioid-naïve patient would be 2.5 - 5mg oramorph 4 hourly/ prn, or s/c morphine where the oral route is not viable (studies indicate no difference of efficacy between routes). Codeine could be used as an alternative in opioid naive patients.
- No studies have examined the difference between a slow and immediate release preparation.
- There is no evidence for a ceiling dose of opioids, and dose escalation should be based on clinical judgement.
• There is no specific evidence for oxycodone in breathlessness, but extrapolating from the above studies there appears to be a group effect and a trial of oxycodone would be a reasonable alternative in patients who are intolerant of morphine.

• For patients already on opioids for other indications such as pain, there is no clear evidence as to whether the prn dose for breathlessness should be the same as for pain. Many of the studies included have used 1/6th of total daily opioids dose where patients are already on opioids, and conclude this to be effective. Expert opinion, such as Twycross advocates a dose of 100% of prn dose if breathlessness severe, 50-100% of prn dose if breathlessness moderate, and 25-50% of prn dose if breathlessness mild.

Benzodiazepines

The Cochrane review of 2010 concludes that there is no evidence for a beneficial effect of benzodiazepines for the relief of breathlessness in patients with advanced cancer and COPD. There is a slight but non-significant trend towards a beneficial effect but the overall effect size is small. The review recommends consideration of benzodiazepines as a second or third line treatment when opioids and non-pharmacological measures have failed to control breathlessness. No safety concerns were identified. After completion of our literature search, a further RCT has been published comparing oral morphine and oral midazolam, which supports the use of midazolam for breathlessness.

1) Diazepam – 1 small RCT showed some improvement in exercise tolerance, but none in breathlessness, when diazepam was compared with placebo. 2 small cases studies failed to show convincing improvement in breathlessness.

2) Midazolam – 2 RCTs both showed an improvement in breathlessness with midazolam; one which compared midazolam vs morphine vs combination of both and found the combination arm to be significantly more effective than either alone. The second paper found midazolam to be as efficacious as morphine at rest, and superior during ambulation.

Clinical advice for benzodiazepines:

Clinical experience, and some evidence, suggests that benzodiazepines can be helpful in breathlessness, particularly in combination with opioids, and in patients with a significant anxiety component. The exact choice will depend on route of administration and onset of action, but typical starting doses would be lorazepam 0.5-1mg SL, diazepam 2-10 mg, or midazolam 2.5-5mg prn or 5-10mg via syringe driver over 24 hours if oral route not available.

Oxygen & Heliox

There is a Cochrane review, 3 further systematic reviews and 1 cohort study looking at oxygen in a mix of malignant and non-malignant disease, in which many of the same papers are evaluated. In the majority of studies, there was no benefit to oxygen as compared with air in terms of dyspnoea scores and exercise capacity. However some sub-groups of patients did seem to derive more benefit:

- Hypoxic patients
- Kyphoscoliotic patients who desaturated on exertion

Since completing the literature searching a subsequent multi-centre RCT has been published. This confirmed that oxygen did not offer any symptomatic benefit over the use of air for palliative patients with breathlessness and a PaO2 >7.3kPa.

There is 1 RCT looking at heliox for dyspnoea in lung cancer. Heliox was found to be superior to O2 and air for exercise capacity and sats, but only superior to air for improving dyspnoea scores. Heliox is more commonly used in the setting of airway obstruction, as it is ‘less dense and viscous than air and its use helps reduce the respiratory work required when there is high ventilatory demand or upper airway obstruction’.

Clinical advice for oxygen & heliox:

- Clinical experience suggests that many patients may gain as much benefit from a fan than oxygen.
- Oxygen itself can be burdensome in terms of limiting mobility, mucosal drying, communication, risks in smokers etc. Risks and benefits should be weighed up for individual patients during a trial period.
- Hypoxic (sats <88%) patients are most likely to benefit from oxygen. Usual caution should be taken in patients at risk of CO2 retention.
- Patients do not need to remain on oxygen for prolonged periods of time (as in LTOT for COPD)
- In terminal illness, oxygen should be given for symptomatic relief rather than specifically to correct low sats (and therefore regular assessment of sats/blood gases is not required).
- Heliox is not routinely used in the setting of chronic breathlessness due to lack of availability and lack of familiarity with its use for this indication. It can be used in an emergency setting in upper airway obstruction while more definitive treatment is arranged.

Steroids

There is no clear evidence to support the use of steroids for breathlessness of unknown cause, however a number of clinical guidelines (level 4 evidence only) suggest a trial dose of 4-8mg dexamethasone for this situation. It is likely that patients with an underlying inflammatory cause for their breathlessness are more likely to benefit.

For obstruction of a hollow viscus (Stridor, SVCO etc) the PCF recommends dexamethasone 16mg daily. This is supported by a case series of 3 patients with clear clinical signs of upper airway obstruction in which up to 10mg IV 6hourly was used, with rapid response.

Clinical advice for steroids:

- Start 16mg dexamethasone daily in patients with obstruction of a hollow viscus as above. In the emergency setting higher doses could be used.
- For patients with breathlessness of unknown cause a trial of 4-8mg dexamethasone can be tried, if felt clinically appropriate. If there is no
symptomatic improvement in 4 days, steroids should be stopped, in view of significant side effect profile of continuing treatment.

Nabilone

Benefit was reported in a single case report\textsuperscript{48}. The findings were not replicated in a much larger (n=132) prospective study\textsuperscript{49} and therefore nabilone cannot be recommended for the symptomatic relief of breathlessness.

Other nebulised therapies

1) Furosemide

An initial case series\textsuperscript{50} (level 3 evidence) have shown promise for the use of nebulised furosemide, but this was only replicated in one of the three small RCTs\textsuperscript{51-53}.

2) Lidocaine (Lignocaine)

The one trial\textsuperscript{54} comparing nebulised lignocaine vs saline showed a small improvement in the distress of breathing for saline, but an increase in distress with lignocaine. Rated effort of breathing was reduced in both groups.

3) Saline

2 RCTs\textsuperscript{55-56} performed in patients with advanced COPD showed significant improvement in breathlessness scores following administration of nebulised saline.

Clinical advice: Other nebulised therapies:

- Nebulised saline is the only drug supported by evidence for relief of dyspnoea without reversible broncho-constriction. It may be a safer alternative with fewer side effects for patients who do not specifically respond to nebulised b-agonist therapy.
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<th>N</th>
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<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
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<tr>
<td>1†</td>
<td>Eiser</td>
<td>1991</td>
<td>COPD</td>
<td>10</td>
<td>RCT DB</td>
<td>Oral diamorphine vs placebo</td>
<td>VAS</td>
<td>No sig. effect on breathlessness ct placebo. (Note poor oral bioavailability)</td>
</tr>
<tr>
<td>1†</td>
<td>Bruera</td>
<td>1993</td>
<td>Cancer patients on stable opioid</td>
<td>9</td>
<td>RCT DB</td>
<td>SC morphine vs placebo</td>
<td>VAS</td>
<td>VAS improved from 30-14 (stat sig)</td>
</tr>
<tr>
<td>1</td>
<td>Light</td>
<td>1996</td>
<td>COPD patients, FEV1 &lt;0.5</td>
<td>7</td>
<td>Crossover study</td>
<td>Intervention: 30mg morphine PO or 30mg morphine plus 10mg prochlorperazine or 30mg morphine + 25 mg promethazine vs placebo</td>
<td>Exercise capacity (EC), psychological status</td>
<td>No significant improvement in EC with morphine alone, but improvement with morphine + promethazine. No difference in subjective mental state</td>
</tr>
<tr>
<td>1†</td>
<td>Poole</td>
<td>1998</td>
<td>Severe COPD</td>
<td>16</td>
<td>RCT DB</td>
<td>6wk MST 10-20mg bd vs placebo</td>
<td>CRQ</td>
<td>No sig difference in dyspnoea subscale. Mastery subscale worse on morphine. Exercise tolerance better on placebo</td>
</tr>
<tr>
<td>1†</td>
<td>Mazzocato</td>
<td>1999</td>
<td>Elderly patients, Cancer, COPD, CHF</td>
<td>9</td>
<td>RCT DB</td>
<td>5mg sc morphine vs placebo</td>
<td>VAS, BORG scale</td>
<td>Stat sig improvement with morphine. Effect sustained for up to 120mins. VAS from 57.8-32.8</td>
</tr>
<tr>
<td>1†</td>
<td>Johnson</td>
<td>2002</td>
<td>NYHA III or IV</td>
<td>10</td>
<td>Randomised, cross over placebo controlled</td>
<td>5mg (2.5mg if creat &gt;200) oral morphine qds 4/7 vs placebo</td>
<td>dyspnoea on 100mm VAS, pulse, RR, and BP, SE’s, QOL scores</td>
<td>Improvement in dyspnoea, but no significant changes in quality of life scores</td>
</tr>
<tr>
<td>1</td>
<td>Williams</td>
<td>2003</td>
<td>Stable CHF</td>
<td>16</td>
<td>Randomised double blind placebo</td>
<td>1-2mg IV diamorphine vs placebo prior to exercise</td>
<td>CPEx, tidal volume, RR, SOB not measured</td>
<td>Diamorphine improved oxygen consumption, but not exercise duration.</td>
</tr>
<tr>
<td>1+</td>
<td>Abernethy</td>
<td>2003</td>
<td>Patients from respiratory, cardiac, general, and palliative medicine OP</td>
<td>48</td>
<td>Randomised placebo controlled trial</td>
<td>20mg modified release morphine od for 4/7 vs placebo for 4/7</td>
<td>VAS, exercise tolerance (MRC scale) RR, BP, HR, sats, sleep disturbance, SE’s</td>
<td>Significant improvement in VAS, reduced sleep disturbance.</td>
</tr>
<tr>
<td>1†</td>
<td>Bruera</td>
<td>2005</td>
<td>Cancer patients on opioids</td>
<td>11</td>
<td>RCT DB</td>
<td>Morphine sc with placebo neb vs morphine neb with sc placebo</td>
<td>VAS, 0-10 scale for dyspnoea</td>
<td>Insufficiently powered to detect diff. between groups. Improved scores in both groups</td>
</tr>
<tr>
<td>3†</td>
<td>Allen</td>
<td>2005</td>
<td>Elderly patients; IPF &amp; severe SOB</td>
<td>11</td>
<td>Open observational</td>
<td>Diamorphine 2.5mg (&lt;60kg,) 5mg (&gt;60kg) subcut.</td>
<td>VAS, Sats</td>
<td>Stat sig improvement in VAS mean 83-36.</td>
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### Summary of Studies that evaluated nebulised opioids for the treatment of dyspnoea in the palliative care population

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<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
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<tbody>
<tr>
<td>1-</td>
<td>Young*</td>
<td>1989</td>
<td>Advanced Chronic lung disease</td>
<td>11</td>
<td>Randomised, double-blind, crossover, placebo controlled</td>
<td>Low dose neb morphine vs placebo</td>
<td>Exercise endurance</td>
<td>Improved exercise endurance - 2 pat results skewed results (later reported in 5)</td>
</tr>
<tr>
<td>1-</td>
<td>Beauford*</td>
<td>1993</td>
<td>COPD</td>
<td>8</td>
<td>Randomised, double-blind, crossover, placebo controlled</td>
<td>Neb Morphine 0mg or 1mg or 4mg or 10mg.</td>
<td>Exercise testing, motor speed, mood, visual vigilance. Before and after 45mins.</td>
<td>No significant difference between morphine and placebo.</td>
</tr>
<tr>
<td>Level</td>
<td>First author*</td>
<td>Year</td>
<td>Subjects</td>
<td>N</td>
<td>Design</td>
<td>Intervention</td>
<td>Evaluation</td>
<td>Results</td>
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<tr>
<td>1-</td>
<td>Masood⁵⁷</td>
<td>1995</td>
<td>Severe COPD</td>
<td>12</td>
<td>Randomised, double-blind, crossover.</td>
<td>Neb morphine vs iv morphine vs placebo</td>
<td>Dyspnoea scale, exercise tolerance, gas exchange during exercise.</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>1-</td>
<td>Jankelson⁶⁸</td>
<td>1997</td>
<td>Stable COPD</td>
<td>16</td>
<td>Randomised, double-blind, cross-over</td>
<td>Neb high dose morphine (40mg) vs low dose morphine (20mg) vs saline</td>
<td>Breathlessness on exercise before and 1hr after treatment, serum morphine levels</td>
<td>No difference in exercise induced breathlessness with higher dose morphine</td>
</tr>
<tr>
<td>1-</td>
<td>Noseda⁵⁹</td>
<td>1997</td>
<td>Various chest disease</td>
<td>17</td>
<td>Double-blind cross over, placebo controlled</td>
<td>Morphine (various doses) vs saline, with and without O2.</td>
<td>Dyspnoea scale (VAS), O2 sats, RR, at end of nebulisation and 10 mins later.</td>
<td>No difference in dyspnoea between treatment groups.</td>
</tr>
<tr>
<td>2-</td>
<td>Coyne¹¹</td>
<td>2002</td>
<td>Oncology inpatients with dyspnoea</td>
<td>35</td>
<td>Uncontrolled study</td>
<td>Neb fentanyl citrate + saline</td>
<td>Dyspnoea, O2 saturations, RR</td>
<td>Dyspnoea improved in 26/32 patients. 3 patients dropped out. O2 sats and RR improved at 5 mins. No S/E reported</td>
</tr>
<tr>
<td>1-</td>
<td>Bruera²⁶</td>
<td>2005</td>
<td>Primary or secondary lung cancer patients with dyspnoea at rest &gt;3/10</td>
<td>11</td>
<td>Double blind, randomised controlled trial</td>
<td>Neb vs sc morphine</td>
<td>Dyspnoea score 1 hr post treatment</td>
<td>No sig difference found, small numbers. More side effects with sc morphine. Patients preferred neb route</td>
</tr>
<tr>
<td>1-</td>
<td>Charles²⁷</td>
<td>2008</td>
<td>Primary or secondary lung cancer. Some pts also had COPD.</td>
<td>25</td>
<td>Double blind, randomised, placebo controlled, cross over</td>
<td>Neb saline vs neb hydromorphone vs systemic hydromorphone</td>
<td>Dyspnoea rating (VAS), patient choice.</td>
<td>All treatments reduced dyspnoea. Only neb hydromorphone produced statis sig reduction in 1 point on 10 point VAS after 10 mins. Patient choice: Equal numbers for each treatment.</td>
</tr>
<tr>
<td>1-</td>
<td>Polosa²⁸</td>
<td>2009</td>
<td>Interstitial lung disease</td>
<td>6</td>
<td>RCT double blind crossover</td>
<td>2.5-5mg Neb morphine vs placebo</td>
<td>Dyspnoea score, &amp; various other indices 30mins post nebulisation during and after exercise</td>
<td>No difference between interventions</td>
</tr>
</tbody>
</table>

Summary of Studies that evaluated fentanyl for the treatment of dyspnoea in the palliative care population

<table>
<thead>
<tr>
<th>Level</th>
<th>First author*</th>
<th>Year</th>
<th>Subjects</th>
<th>N</th>
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<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-</td>
<td>Coyne¹¹</td>
<td>2002</td>
<td>Cancer pts with dyspnoea</td>
<td>35</td>
<td>Cohort</td>
<td>Nebulised fentanyl 25mcg</td>
<td>RR, sats, subjective report</td>
<td>Reduction in RR, and subjective improvements in dyspnoea</td>
</tr>
<tr>
<td>Level</td>
<td>First author*</td>
<td>Year</td>
<td>Subjects</td>
<td>N</td>
<td>Design</td>
<td>Intervention</td>
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<tr>
<td>3</td>
<td>Clemens*3</td>
<td>2007</td>
<td>Palliative care inpatients with cancer</td>
<td>11</td>
<td>Prospective non-randomised trial</td>
<td>Normal treatment, oramorph or IR hydromorphone</td>
<td>RR, sats, dyspnoea score at rest and exercise</td>
<td>Opioids stat improved dyspnoea c/f normal treatment</td>
</tr>
<tr>
<td>1</td>
<td>Charles*2</td>
<td>2008</td>
<td>Palliative care patients</td>
<td>20</td>
<td>PILOT double blinded RCT cross over study</td>
<td>Hydromorphone, nebulised, oral or subcut vs placebo</td>
<td>RR, HR, oxygen sats, 10 point VAS</td>
<td>VAS improved with all interventions, but only clinically significant in neb hydromorphone arm. No stat. difference between arms</td>
</tr>
<tr>
<td>3</td>
<td>Clemens*4</td>
<td>2008</td>
<td>Cancer patients with terminal illness</td>
<td>46</td>
<td>Prospective non-randomised study</td>
<td>4h IR morphine or hydromorphone</td>
<td>Dyspnoea score (1-100), sats, RR</td>
<td>Significant. fall in dyspnoea score post opioid</td>
</tr>
<tr>
<td>3</td>
<td>Clemens*5</td>
<td>2008</td>
<td>25 terminal cancer &amp; 2 ALS</td>
<td>27</td>
<td>Prospective non-randomised study</td>
<td>4h IR morphine or hydromorphone</td>
<td>Dyspnoea score (1-100), sats, RR</td>
<td>Significant. fall in dyspnoea score post opioid</td>
</tr>
<tr>
<td>3</td>
<td>Clemens*1</td>
<td>2008</td>
<td>Cancer patients with dyspnoea</td>
<td>14</td>
<td>Prospective non-randomised trial</td>
<td>Oral hydromorphone</td>
<td>RR, sats, 10 pt numeric rating scale</td>
<td>Reported improvement in breathlessness score at rest &amp; exertion and RR</td>
</tr>
</tbody>
</table>
### Summary of Studies that evaluated Dihydro/Codeine for the treatment of dyspnoea in the palliative care population

<table>
<thead>
<tr>
<th>Level</th>
<th>First author*</th>
<th>Year</th>
<th>Subjects</th>
<th>N</th>
<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-</td>
<td>Chua**</td>
<td>1997</td>
<td>Chronic heart failure NYHA II &amp; III</td>
<td>12</td>
<td>Men only</td>
<td>Double-blind RCT Placebo vs dihydrocodeine (DHC) (1mg/kg body weight)</td>
<td>Chemosensitivity assessment, CPEX, dyspnoea scores and fatigue using modified Borg scale</td>
<td>DHC improved exercise tolerance</td>
</tr>
<tr>
<td>1-</td>
<td>Woodcock**</td>
<td>1981</td>
<td>COPD, moderate to severe SOB on exertion</td>
<td>12</td>
<td>Double-blind RCT</td>
<td>Caffeine (anhydrous, 5mg/kg) vs Alcohol (vodka, 1ml/kg) Dihydrocodeine (1mg/kg)</td>
<td>FEV1, forced VC, exercise tolerance, ABG, Grade of dyspnoea</td>
<td>DHC reduced breathlessness by 20%, exercise tolerance increased by 18%. Greatest improvement when DHC combined with O2 - 32%</td>
</tr>
<tr>
<td>1-</td>
<td>Johnson**</td>
<td>1983</td>
<td>COPD with severe breathlessness</td>
<td>18</td>
<td>Double-blind RCT</td>
<td>Dihydrocodeine 15mg PRN (TDS) 30mins prior to exercise vs placebo</td>
<td>PEFR, FEV1, FVC, VAS score &amp; exercise tolerance &amp; mobility</td>
<td>DHC increased walk distance by 16-17%, VAS reduced by up to 17.8%</td>
</tr>
<tr>
<td>1-</td>
<td>Rice**</td>
<td>1987</td>
<td>Moderate COPD</td>
<td>11</td>
<td>Double-blind cross over RCT</td>
<td>Codeine 30mg QDS vs Promethazine 25mg QDS</td>
<td>FEV1, FVC, ABG, Exercise performance (12 min walk), breathlessness (VAS)</td>
<td>No significant improvement in breathlessness or exercise tolerance</td>
</tr>
</tbody>
</table>

### Summary of Studies that evaluated benzodiazepines for the treatment of dyspnoea in the palliative care population

<table>
<thead>
<tr>
<th>Level</th>
<th>First author*</th>
<th>Year</th>
<th>Subjects</th>
<th>N</th>
<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Mitchell-Heggs**</td>
<td>1980</td>
<td>Severe COPD</td>
<td>4</td>
<td>Case series</td>
<td>25mg Diazepam daily</td>
<td>pCO2, pO2, PH, Spirometry, Serum diazepam</td>
<td>Much improved level of function, no change pO2 pCO2</td>
</tr>
<tr>
<td>1-</td>
<td>Woodcock**</td>
<td>1981</td>
<td>Severe COPD</td>
<td>18</td>
<td>Double blind cross over RCT</td>
<td>Diazepam 25mg/day Vs Promethazine 125mg/day vs Placebo</td>
<td>PEFR, FEV1, FVC, pO2, pCO2, PH, Spirometry, breathlessness score, exercise tests.</td>
<td>No change observations. Non-sig. improvement breathlessness score. Reduced exercise tolerance</td>
</tr>
<tr>
<td>3</td>
<td>Sen**</td>
<td>1983</td>
<td>Moderate – Severe COPD</td>
<td>3</td>
<td>Case Series</td>
<td>Diazepam increased in 5mg increments daily</td>
<td>Exercise tolerance (in yards)</td>
<td>Patients too drowsy to continue on diazepam. Nr benefit to exercise tolerance</td>
</tr>
<tr>
<td>1-</td>
<td>Eimer**</td>
<td>1985</td>
<td>COPD</td>
<td>5</td>
<td>Double blind cross over RCT</td>
<td>Clorazepate 7.5mg or 22.5mg nocte or placebo</td>
<td>Dyspnoea scale 1-6, walking test</td>
<td>No benefit found</td>
</tr>
<tr>
<td>1-</td>
<td>Man**</td>
<td>1986</td>
<td>COPD</td>
<td>29</td>
<td>Double blind cross over RCT</td>
<td>Alprazolam 0.5mg BD or placebo</td>
<td>VAS 1-5, at rest &amp; exercise, 12 MWT</td>
<td>No benefit found</td>
</tr>
<tr>
<td>1-</td>
<td>Shivram**</td>
<td>1989</td>
<td>COPD</td>
<td>12</td>
<td>Double blind cross over RCT</td>
<td>Alprazolam 0.25mg tds or placebo for 2 weeks</td>
<td>Borg scale, sats</td>
<td>No benefit found</td>
</tr>
</tbody>
</table>
1- Navigante et al. 2006 Terminal cancer 101 Single-blinded randomized 2.5mg morphine every 4h vs 5mg midazolam every 4h vs 2.5mg morphine + 5mg midazolam every 4h Vital signs, Modified Borg, subjective report, episodes rescue medication Reduction in dyspnoea in all groups, largest effect in combination group

1- Navigante et al. 2010 Advanced cancer 63 Single-blinded randomized 2mg midazolam vs 3 mg morphine (PO), titrated until 50% reduction in SOB Sats, dyspnoea scale (1-10) Sig. reduction in dyspnoea in both groups, more marked in midazolam group. No withdrawals due SEs. Sats unaffected

Summary of Studies that evaluated oxygen for the treatment of dyspnoea in the palliative care population

<table>
<thead>
<tr>
<th>Level</th>
<th>First author*</th>
<th>Year</th>
<th>Subjects</th>
<th>N</th>
<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>Booth*</td>
<td>2004</td>
<td>Cancer, COPD, CHF</td>
<td>629</td>
<td>Systematic review of RCTs</td>
<td>O2 vs air, at rest or exertion depending on study</td>
<td>Borg, VAS, numerical scale, endurance</td>
<td>1/5 +ve for O2 at rest in COPD, 19/22 +ve for either endurance or dyspnoea in COPD. Mixed results in advanced cancer, and no benefit seen in CHF</td>
</tr>
<tr>
<td>1+</td>
<td>Uronis*</td>
<td>2008</td>
<td>Cancer pts</td>
<td>148</td>
<td>Systematic review</td>
<td>4 x O2 vs air, 1 x O2 vs air vs heliox</td>
<td>Mod Borg, VAS, numerical scale 0-10</td>
<td>Failed to improve dyspnoea 2/5 improved 6MWT</td>
</tr>
<tr>
<td>1++</td>
<td>Cranston* (Cochrane review)</td>
<td>2008</td>
<td>Cancer pts, CHF, kyphoscoliosis</td>
<td>144</td>
<td>Meta-analysis / systematic review of RCTs</td>
<td>8 cross-over studies; 5 = O2 at rest, 3 = O2 vs air on exercise</td>
<td>Mod Borg, VAS, numerical scale</td>
<td>Failed to demonstrate a consistent benefit of oxygen over air except in kyphoscoliosis and hypoxia</td>
</tr>
<tr>
<td>1+</td>
<td>Ben-Aharon*</td>
<td>2008</td>
<td>Cancer patients</td>
<td>149</td>
<td>Systematic review RCTs</td>
<td>1 x Heliox vs O2 vs air, 5 x O2 vs air</td>
<td>Mod BORG, VAS, numerical scale</td>
<td>Failed to improve dyspnoea except in hypoxic patients</td>
</tr>
<tr>
<td>2-</td>
<td>Currow*</td>
<td>2009</td>
<td>Cancer patients, respiratory and cardiac disease</td>
<td>413</td>
<td>Consecutive cohort study</td>
<td>Face-to-face assessments pre and post home oxygen</td>
<td>0-10 numerical scale</td>
<td>Non-significant improvement in dyspnoea in 150 patients</td>
</tr>
<tr>
<td>1+</td>
<td>Abernethy*</td>
<td>2010</td>
<td>Various diagnoses with breathlessness, PaO2&gt;7.3</td>
<td>239</td>
<td>Multi-centre, double-blind, RCT</td>
<td>LTOT vs room air , 15 hours/day for 7 days</td>
<td>Numerical scale 0-10, functional impact, anxiety, McGill QoL Questionnaire, drowsiness, nasal irritation</td>
<td>No difference between the groups.</td>
</tr>
</tbody>
</table>
# Summary of Studies that evaluated steroids for the treatment of dyspnoea in the palliative care population

<table>
<thead>
<tr>
<th>Level</th>
<th>First author</th>
<th>Year</th>
<th>Subjects</th>
<th>N</th>
<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-</td>
<td>Viola</td>
<td>2008</td>
<td>Advanced cancer patients</td>
<td>n/a</td>
<td>Systematic literature review</td>
<td>4 drug classes inc. corticosteroids</td>
<td>No controlled trials identified</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Elsayem</td>
<td>2007</td>
<td>Cancer with upper airway obstruction</td>
<td>3</td>
<td>Case series</td>
<td>IV dex 10mg 6 hourly; IV methylprednisolone 125mg 6hourly; IV dex 10mg 6 hourly</td>
<td>0-10 score in 2 cases Clinical assessment in 1 case</td>
<td>Scores 8-10/10 reduced to 1-2/10 within 12 hrs. Clinical resolution of stridor in final case.</td>
</tr>
<tr>
<td>3</td>
<td>Hardy</td>
<td>2001</td>
<td>Advanced malignant disease</td>
<td>15</td>
<td>Prospective survey</td>
<td>Clinical assessment of response</td>
<td>5/13 better; 6/13 no change; 2/13 worse</td>
<td></td>
</tr>
</tbody>
</table>

# Summary of Studies that evaluated Nabilone for the treatment of dyspnoea in the palliative care population

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Subjects</th>
<th>N</th>
<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmedazai</td>
<td>1988</td>
<td>Case study</td>
<td>1</td>
<td>Case study</td>
<td>Nabilone 0.5mg 12 hrly</td>
<td>Clinical</td>
<td>Breathlessness and anxiety improved</td>
</tr>
<tr>
<td>Maida</td>
<td>2008</td>
<td>Palliative care patients with cancer</td>
<td>112</td>
<td>Prospective observational study</td>
<td>Nabilone 0.5-1mg initially, average dose at end 1.79mg</td>
<td>ESAS</td>
<td>No significant improvement in breathlessness rating</td>
</tr>
</tbody>
</table>

# Summary of Studies that evaluated other nebulised therapies for the treatment of dyspnoea in the palliative care population

<table>
<thead>
<tr>
<th>Level</th>
<th>First author</th>
<th>Year</th>
<th>Subjects</th>
<th>N</th>
<th>Design</th>
<th>Intervention</th>
<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-</td>
<td>Poole</td>
<td>1998</td>
<td>Severe COPD</td>
<td>18</td>
<td>Randomised, double blind, crossover</td>
<td>Nebulised saline vs nebulised terbutaline</td>
<td>FEV1, FVC, Breathlessness on Likert scale and VAS</td>
<td>Breathlessness improved in both groups, but more in terbutaline group (thought to relate to inc. FEV1)</td>
</tr>
<tr>
<td>1-</td>
<td>Khan</td>
<td>2004</td>
<td>COPD patients</td>
<td>34</td>
<td>Single blind, randomised, placebo controlled (N=6 crossover)</td>
<td>Nebulised saline via efficient nebuliser vs inefficient nebuliser</td>
<td>FEV1, FVC, breathlessness (7 point Likert scale), benefit score (7 point scale)</td>
<td>Statistically significant improvement in breathlessness in active group without bronchodilator effect</td>
</tr>
<tr>
<td>3</td>
<td>Shimoyama</td>
<td>2002</td>
<td>Terminal stage cancer with breathlessness</td>
<td>3</td>
<td>Case series</td>
<td>Nebulised furosemide 20mg QDS</td>
<td>VAS</td>
<td>VAS reduced by 5-9 points, sustained effect for 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Author</td>
<td>Year</td>
<td>Study Description</td>
<td>Study Design</td>
<td>Intervention</td>
<td>Endpoint</td>
<td>Results</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>1-</td>
<td>Stone</td>
<td>2002</td>
<td>Terminal stage cancer with breathlessness</td>
<td>Pilot RCT - Double blind, randomized, placebo controlled, cross over</td>
<td>Neb furosemide vs saline</td>
<td>VAS</td>
<td>Trend to worsening VAS, not statistically sig. Pilot finished early</td>
<td></td>
</tr>
<tr>
<td>2-</td>
<td>Kohara</td>
<td>2003</td>
<td>Cancer patients with breathlessness</td>
<td>Uncontrolled, open study</td>
<td>Neb furosemide 20mg</td>
<td>Cancer dyspnoea scale 0min and 60 min</td>
<td>12 patients reported reduced anxiety and effort to breath</td>
<td></td>
</tr>
<tr>
<td>3-</td>
<td>Ong</td>
<td>2004</td>
<td>Moderate-severe COPD</td>
<td>Double blind, randomised, crossover</td>
<td>Neb furosemide 40mg vs saline</td>
<td>VAS during exercise – incremental and constant rate</td>
<td>VAS lower with furosemide – stat sig with constant rate exercise</td>
<td></td>
</tr>
<tr>
<td>4-</td>
<td>Wilcock</td>
<td>2008</td>
<td>Primary/secondary Lung cancer with breathlessness</td>
<td>Double blind, randomised, crossover</td>
<td>Neb furosemide 40mg vs saline vs no treatment</td>
<td>Dyspnoea rating scale, number reading test, arm exercise</td>
<td>No difference between arms</td>
<td></td>
</tr>
<tr>
<td>5-</td>
<td>Wilcock</td>
<td>1994</td>
<td>Cancer with breathlessness</td>
<td>Unblinded, cross over</td>
<td>Neb saline vs low dose lignocaine vs higher dose lignocaine</td>
<td>VAS o,10, 20, 30 &amp; 60 mins</td>
<td>VAS reduced after all treatments. Distress of breathing increased with lignocaine</td>
<td></td>
</tr>
</tbody>
</table>

5) Glossary:

- ABG: Arterial blood gas
- BD: Bis die (twice daily)
- Borg: Scale for rate of perceived exertion
- CHF: Chronic heart failure
- COPD: Chronic obstructive pulmonary disease
- CPEX: Cardiopulmonary exercise testing
- CRQ: Chronic respiratory questionnaire
- DHC: Dihydrocodeine
- ESAS: Edmonton Symptom Assessment System
- FEV1: Forced expiratory volume in 1 second
- FVC: Forced vital capacity
- HR: Heart rate
- IR: Immediate release
- IV: Intravenous
- LTOT: Long term oxygen therapy
- MND: Motor neurone disease
- O2: Oxygen
- OTFC: Oral transmucosal fentanyl citrate
- PCF: Palliative Care Formulary
- PEFR: Peak expiratory flow rate
- PRN: Pro re nata (as required)
- QDS: Quarter die sumendum (four times a day)
- RCT: Randomised controlled trial
- RR: Respiratory rate
- Sats: Saturations
- SC: Subcutaneous
- Sig: Significantly
- SL: Sublingual
- SR: Sustained release
- Stat: Statistically
- SVCO: Superior vena cava obstruction
- TDS: Ter die sumendum (three times a day)
- VC: Vital capacity
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Clemens KE, Klaschik E. Symptomatic therapy of dyspnea with strong opioids and it’s effect on ventilation in palliative care patients. J Pain Sympt Manage 2007; 33(4): 473-481

Clemens KE, Quednau I, Klaschik E. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. Supportive Care Cancer 2009; 17:367-377

Clemens KE, Quednau I, Klaschik E. Is there a higher risk of respiratory depression in opioid-naïve palliative care patients during symptomatic therapy of dyspnoea with strong opioids. J Palliat Med 2008; 11(2): 204-216


Abernathy AP, McDonald CF, Frith PA et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet* 2010; 376: 784-93


58 Light RW, Stansbury DW & Webster JS. Effect of 30 mg of Morphine Alone or With Promethazine or Prochlorperazine on the Exercise Capacity of Patients with COPD. *Chest* 1996; 109:975-81

59 Poole PJ, Veale AG, Black PN. The Effect of Sustained-Release Morphine on Breathlessness and Quality of Life in Severe Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 1998; 157 (6 Pt1): 1877-80


62 Currow DC, Kenny B, McDonald C et al. ‘Multi-site open label dose ranging study to determine the minimum effective dose of sustained release morphine (SRM) for reducing refractory breathlessness’. Abstract available in *Eur J Palliative Care* 2009. EAPC 11th Congress 2009 Abstracts. *(Full paper in press)*


Appendix 1

**Search Strategy**

A systematic search of the Cochrane library, Medline and EMBASE was performed, for papers published between 1960 and 2010. The last electronic search was completed July 2010.

The search population was identified using search terms ‘breathless*’, ‘heart failure’, ‘neoplasm’, ‘cancer’, ‘palliative’, ‘hospice’, ‘terminal*’, ‘advanced disease’ and ‘end stage’ using Boolean terms ‘AND’ and ‘OR’ (Appendix C). Where appropriate, terms were mapped to the search tool thesaurus. Title and author, plus free text searching was included within the search strategy. This core search was in turn combined with individual drug groups and names to identify appropriate papers. Hand searching from the bibliographies identified further relevant papers.

The title and abstracts of those papers identified by the search criterion were reviewed. The most appropriate papers were obtained in full text for more detailed review. Unrelated articles were excluded from detailed analysis.

**Medline search**

breathless*.ti,ab  
OR exp DYSPNEA/  
AND  
HEART FAILURE/dm,dt,rh,th  
OR exp CANCER/[dm=Disease Management, dt=Drug Therapy, rh=Rehabilitation, th=Therapy]  
OR "advanced disease".af  
OR neoplasm*.af  
OR exp PALLIATIVE THERAPY/  
OR palliat*.af  
OR exp HOSPICE/  
OR exp HOSPICE CARE/  
OR exp HOSPICE PATIENT/  
OR exp HOSPICE NURSING/  
OR "end stage".af  
OR termina*.af  
AND  
Target Drug
For the steroid search, additional limits to ‘Human and English language’ were added to refine the criterion.

**Embase Search**

breathless*.ti,ab OR exp DYSPNEA/
AND
exp TERMINAL CARE/
OR exp PALLIATIVE CARE/
OR exp TERMINAL CARE/
OR exp HOSPICE CARE/
OR exp HOSPICES/
OR NEOPLASMS/
OR "advanced disease”.af OR "end stage”.af
AND

Target drug

**Appendix 2**

**Levels of Evidence**

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with very low risk of bias
1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2- Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3 Non-analytic studies, e.g., case reports, case series
4 Expert opinion