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 Keeley[1] on behalf of the SIGN research group (see appendix 2).

Guidelines produced: October 2010

Review date: October 2013

Competing interests: None declared

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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%[2].

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[3]. 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[3].

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[4] 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 a 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[3] 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[29] 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[30] has been published comparing oral morphine and oral midazolam, which supports the use of midazolam for breathlessness.

1) Diazepam – 1 small RCT[31] showed some improvement in exercise tolerance, but none in breathlessness, when diazepam was compared with placebo. 2 small cases studies[32-33] failed to show convincing improvement in breathlessness.

2) Midazolam – 2 RCTs[30,34] 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[34], 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[35], 3 further systematic reviews[36-38] and 1 cohort study[39] 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[40] 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[41] 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'[3].

Clinical advice for oxygen & heliox:

- Clinical experience suggests that many patients may gain as much benefit from a fan than oxygen[42].
- 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[43-45] (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[46] recommends dexamethasone 16mg daily. This is supported by a case series[47] 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[48]. The findings were not replicated in a much larger (n=132) prospective study[49] and therefore nabilone cannot be recommended for the symptomatic relief of breathlessness.

Other nebulised therapies

1) Furosemide

An initial case series[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[51-53].

2) Lidocaine (Lignocaine)

The one trial[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[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.

Summary of Studies that evaluated systemic morphine/ diamorphine for the treatment of dyspnoea in the palliative care population

Level	First author*	Year	Subjects	N	Design	Intervention	Evaluation	Results	
1-	Eiser[57]	1991	COPD	10	RCT double blind crossover placebo	Oral diamorphine vs placebo	VAS	No sig. effect on breathlessness ct placebo. (Note poor oral bioavailability)	
1-	Bruera[6]	1993	Cancer patients on stable opioid	9	RCT double blind crossover placebo	sc morphine vs placebo	VAS	VAS improved from 30-14 (stat sig)	
1-	Light[58]	1996	COPD patients, FEV1 <0.5	7	Crossover study	Intervention: 30mg morphine PO or 30mg morphine plus 10mg prochlorperazine or 30mg morphine + 25 mg promethazine vs placebo	Exercise capacity (EC), psychological status	No significant improvement in EC with morphine alone, but improvement with morphine + promethazine No difference in subjective mental state	
1-	Poole[59]	1998	Severe COPD	16	RCT double blind crossover placebo	6wk MST 10-20mg bd vs placebo	CRQ	No sig difference in dyspnoea subscale. Mastery subscale worse on morphine. Exercise tolerance better on placebo	
1-	Mazzocato[7]	1999	Elderly patients, Cancer, COPD, CHF	9	RCT double blind crossover placebo	5mg sc morphine vs placebo	VAS, BORG scale	Stat sig improvement with morphine. Effect sustained for up to 120mins. VAS from 57.8-32.8	
1-	Johnson[8]	2002	NYHA III or IV	10	Randomised, cross over placebo controlled	5mg (2.5mg if creat >200) oral morphine qds 4/7 vs placebo	dyspnoea on 100mm VAS, pulse, RR, and BP, SE's, QOL scores	Improvement in dyspnoea, but no significant changes in quality of life scores	
1-	Williams[9]	2003	Stable CHF	16	Randomised double blind placebo	1-2mg IV diamorphine vs placebo prior to exercise	CPEX, tidal volume, RR. SOB not measured	Diamorphine improved oxygen consumption, but not exercise duration.	
1+	Abernethy[10]	2003	Patients from respiratory, cardiac, general, and palliative medicine OP	48	Randomised placebo controlled trial	2Omg modified release morphine od for 4/7 vs placebo for 4/7	VAS, exercise tolerance (MRC scale) RR, BP, HR, sats, sleep disturbance, SE's	Significant improvement in VAS, reduced sleep disturbance.	
1-	Bruera[26]	2005	Cancer patients on opioids	11	RCT double blind crossover	Morphine sc with placebo neb vs morphine neb with sc placebo	0-10 scale for dyspnoea	Insufficiently powered to detect diff. between groups. Improved scores in both groups	
3	Allen[60]	2005	Elderly patients; IPF & severe SOB	11	Open observational	Diamorphine 2.5mg (<60kg,) 5mg (>60kg) subcut.	VAS. Sats	Stat sig improvement in VAS mean 83-36.	

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3	Clemens[23]	2007	Palliative care inpatients with cancer	11	Prospective non randomised trial	Normal treatment, oramorph or IR hydromorphone	RR, sats, dyspnoea score at rest and exercise	Opioids stat improved dyspnea c/f normal treatment	
3	Clemens[61]	2008	MND patients	6	Propective,non-randomised pilot study	4h IR morphine PO (2.5mg -20mg)	Dyspnoea & anxiety scores (1-10 scale), sats, RR	Statistically significant fall in dyspnoea & anxiety scores	
3	Clemens[24]	2008	Cancer patients with terminal illness	46	Prospective non-randomised study	4h IR morphine or hydromorphone	Dyspnoea score (1-100), sats, RR	Statistically significant fall in dyspnoea score post opioid	
3	Clemens[25]	2008	All patients with terminal illness (25 cancer & 2 ALS)	27	Prospective non-randomised study	4h IR morphine or hydromorphone	Dyspnoea score (1-100), sats, RR	Statistically significant fall in dyspnoea score post opioid	
2-	Currow[62]	2009	48/68 = COPD	68	Open label, dose finding long term clinical study	Morphine SR 10-30mg od	VAS for dyspnoea	51% found sufficient benefit to continue 12% drowsiness	
2-	Wiese[63]	2009	Palliative cancer patients with 'acute dyspnoea' All on a strong opioid for pain	116	Retrospective multicentre	Treatment groups: 1) morphine + 02; 2) morphine + 02 + bronchodilator; 3) bronchodilator + 02; 4) 02 alone; 5) No medical tx; 6) changed tracheostomy	Symptom score 0-6, sats, RR	Increase in sats & reduction in RR Groups 1 & 2. Improved symptom scores in all groups, but improvement in Groups 1+2 greater than in group 3+4	

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

Level	First author*	Year	Subjects	N	Design	Intervention	Evaluation	Results	
1-	Young[64]	1989	Advanced Chronic lung disease	11	Randomised, double-blind, crossover, placebo controlled	Low dose neb morphine vs placebo	Exercise endurance	Improved exercise endurance - 2 pat results skewed results (later reported in [5]	
1-	Beauford[65]	1993	COPD	8	Randomised, double-blind, crossover, placebo controlled	Neb Morphine 0mg or 1mg or 4mg or 10mg.	Exercise testing, motor speed, mood, visual vigilance. Before and after 45mins.	No significant difference between morphine and placebo.	

3	Farncombe[66]	1994	Varying chest diseases - terminal stages	54	Retrospective chart review of patients given neb opioids for dyspnoea	Morphine, or hydromorphone or codeine - regular doses. Length of treatment 1day to >15 days. 81% had more than 3 doses.	Dyspnoea, exercise tolerance	63% favourable results - reduced dyspnoea, increased exercise endurance and feeling more relaxed. Effect obtained within 15mins. Lasted >4hrs in over half pts.	
1-	Masood[67]	1995	Severe COPD	12	Randomised, double-blind, crossover.	Neb morphine vs iv morphine vs placebo	Dyspnoea scale, exercise tolerance, gas exchange during exercise.	No significant difference between groups	
1-	Jankelson[68]	1997	Stable COPD	16	Randomised, double-blind, cross-over	Neb high dose morphine (40mg) vs low dose morphine (20mg) vs saline	Breathlessness on exercise before and 1hr after treatment, serum morphine levels	No difference in exercise induced breathlessness with higher dose morphine	
1-	Noseda[69]	1997	Various chest disease	17	Double-blind cross over, placebo controlled	Morphine (various doses) vs saline, with and without O2.	Dyspnoea scale (VAS), O2 sats, RR, at end of nebulisation and 10 mins later.	No difference in dyspnoea between treatment groups.	
2-	Coyne[11]	2002	Oncology Inpatients with dyspnoea	35	Uncontrolled study	Neb fentanyl citrate + saline	Dyspnoea, o2 saturations, RR	Dyspnoea improved in 26/32 patients. 3 patients dropped out. O2 sats and RR improved at 5 mins. NO S/E reported	
1-	Bruera[26]	2005	Primary or secondary lung cancer patients with dyspnoea at rest >3/10	11	Double blind, randomised controlled trial	Neb vs sc morphine	Dyspnoea score 1 hr post treatment	No sig difference found, small numbers. More side effects with sc morphine. Patients preferred neb route	
1-	Charles[27]	2008	Primary or secondary lung cancer. Some pts also ahd COPD.	25	Double blind, randomised, placebo controlled, cross over	Neb saline vs neb hydromorphone vs systemic hydromorphone	Dyspnoea rating (VAS), patient choice.	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.	
1-	Polosa[28]	2009	Interstitial lung disease	6	RCT double blind crossover	2.5-5mg Neb morphine vs placebo	Dyspnoea score, & various other indices 30mins post nebulisation during and after exercise	No difference between interventions	

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

Level	First author*	Year	Subjects	N	Design	Intervention	Evaluation	Results	Ove (+ or
2-	Coyne[11]	2002	Cancer pts with dyspnoea	35	Cohort	Nebulised fentanyl 25mcg	RR, sats, subjective report	Reduction in RR, and subjective improvements in dyspnoea	+ve

3	Graff[12]	2004	CF patient with end-stage disease	1	Case report	Nebulised fentanyl 25-50mcg	RR, HR, oxygen sats, modified Borg score	All measurements improved	+ve
1-	Smith[16]	2009	Patients (1 cancer, 1? Diagnosis) with dyspnoea	2	Double-blind, placebo-controlled randomized trial	Nebulised fentanyl (?dose) vs placebo	Dyspnoea score (1-100), sats, RR	Dyspnoea scores improved with fentanyl. No change in sats or RR.	+ve
3	Sitte[13]	2008	Lung cancer, CCF, COPD, pul HT, interstitial lung disease, CRF.	3	Case series	Intranasal fentanyl 50-500mcg	RR, sats	RR and sats improved	+ve
3	Benitez-Rosario[14]	2005	Cancer patients with dyspnoea	4	Case series	OTFC 400-1200mcg	Dyspnoea score (1-10 scale), sats, RR	Dyspnoea score and RR improved, no change in sats	+ve
3	Gauna[15]	2008	COPD, pulmonary fibrosis, metastatic lung cancer	4	Case series	OTFC	Orientation and clock drawing test, dyspnoea score (10 point VAS), RR, sats	Dyspnoea score improved with max improvement at 45 mins. RR and oxygen sats improved.	+ve

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

Level	First author*	Year	Subjects	N	Design	Intervention	Evaluation	Results	O fir (+
3	Clemens[23]	2007	Palliative care inpatients with cancer	11	Prospective non randomised trial	Normal treatment, oramorph or IR hydromorphone	RR, sats, dyspnoea score at rest and exercise	Opioids stat improved dyspnoea c/f normal treatment	+\
1-	Charles[22]	2008	Palliative care patients	20	PILOT double blinded RCT cross over study	Hydromorphone, nebulised, oral or subcut vs placebo	RR, HR, oxygen sats, 10 point VAS	VAS improved with all interventions, but only clinically significant in neb hydromorphone arm. No stat. difference between arms	-v
3	Clemens[24]	2008	Cancer patients with terminal illness	46	Prospective non-randomised study	4h IR morphine or hydromorphone	Dyspnoea score (1-100), sats, RR	Significant. fall in dyspnoea score post opioid	+\ op
3	Clemens[25]	2008	25 terminal cancer & 2 ALS	27	Prospective non-randomised study	4h IR morphine or hydromorphone	Dyspnoea score (1-100), sats, RR	Significant. fall in dyspnoea score post opioid	+\ op
3	Clemens[21]	2008	Cancer patients with dyspnoea	14	Prospective non randomised trial	Oral hydromorphone	RR, sats, 10 pt numeric rating scale	Reported improvement in breathlessness score at rest & exertion and RR	+\

Summary of Studies that evaluated Dihydro/Codeine for the treatment of dyspnoea in the palliative care population

Level	First author*	Year	Subjects	N	Design	Intervention	Evaluation	Results	
1-	Chua[17]	1997	Chronic heart failure NYHA II & III	12 Men only	Double-blind RCT	Placebo vs dihydrocodeine (DHC)(1mg/kg body weight)	Chemosensitivity assessment, CPEX, dyspnoea scores and fatigue using modified Borg scale	DHC improved exercise tolerance	
1-	Woodcock[18]	1981	COPD, moderate to severe SOB on exertion	12	Double-blind RCT	Caffeine (anhydrous, 5mg/kg) vs Alcohol (vodka,1ml/kg) Dihydrocodeine (1mg/kg)	FEV1, forced VC, exercise tolerance, ABG, Grade of dyspnoea	DHC reduced breathlessness by 20% exercise tolerance increased by 18%. Greatest improvement when DHC combined with O2 - 32%	
1-	Johnson[19]	1983	COPD with severe breathlessness	18	Double-blind RCT	Dihydrocodeine 15mg PRN (TDS) 30mins prior to exercise vs placebo	PEFR, FEV1, FVC, VAS score &, exercise tolerance & mobility	DHC increased walk distance by 16-17%, VAS reduced by up to 17.8%	
1-	Rice[20]	1987	Moderate COPD	11	Double-blind cross over RCT	Codeine 30mg QDS vs Promethazine 25mg QDS	FEV1, FVC, ABG, Exercise performance (12 min walk), breathlessness (VAS)	No significant improvement in breathlessness or exercise tolerance	

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

Level	First author	Year	Subjects	N	Design	Intervention	Evaluation	Results	
3	Mitchell-Heggs[32]	1980	Severe COPD	4	Case series	25mg Diazepam daily	pCO2, pO2, PH, Spirometry, Serum diazepam	Much improved level of function, no change pO2 pCO2	
1-	Woodcock[31]	1981	Severe COPD	18	Double blind cross over RCT	Diazepam 25mg/day Vs Promethazine 125mg/day vs Placebo	PEFR, FEV1, FVC, pO2, pCO2, PH, Spirometry, breathlessness score, exercise tests.	No change observations. Non-sig. improvement breathlessness score. Reduced exercise toleran	
3	Sen[33]	1983	Moderate – Severe COPD	3	Case Series	Diazepam increased in 5mg increments daily	Exercise tolerance (in yards)	Patients too drowsy to continue on diazepam. N benefit to exercise tolerance	
1-	Eimer[70]	1985	COPD	5	Double blind cross over RCT	Clorazepate 7.5mg or 22.5mg nocte or placebo	Dyspnoea scale 1-6, walking test	No benefit found	
1-	Man[71]	1986	COPD	29	Double blind cross over RCT	Alprazolam 0.5mg BD or placebo	VAS 1-5, at rest & exercise, 12 MWT	No benefit found	
1-	Shivram[72]	1989	COPD	12	Double blind cross over RCT	Alprazolam 0.25mg tds or placebo for 2 weeks	Borg scale, sats	No benefit found	

1-	Navigante[34]	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 effe combination group	
1-	Navigante[30]	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

Level	First author*	Year	Subjects	N	Design	Intervention	Evaluation	Results	
1+	Booth[36]	2004	Cancer, COPD, CHF	629	Systematic review of RCTs	O2 vs air, at rest or exertion depending on study	Borg, VAS, numerical scale, endurance	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 i CHF	
1+	Uronis[37]	2008	Cancer pts	148	Systematic review	4 x O2 vs air, 1 x O2 vs air vs heliox 3 trials O2 at rest, 2 during 6 min walk	Mod Borg, VAS, numerical scale 0-10	Failed to improve dyspnoea 2/5 improved 6MWT	
1++	Cranston[35] (Cochrane review)	2008	Cancer pts, CHF, kyphoscoliosis	144	Meta-analysis / systematic review of RCTs	8 cross-over studies; 5 = O2 vs air at rest, 3 = O2 vs air on exercise	Mod Borg, VAS, numerical scale	Failed to demonstrate a consistent benefit of oxygen over air except in kyphoscoliosis and hypoxia	
1+	Ben-Aharon[38]	2008	Cancer patients	149	Systematic review RCTs	1 x Heliox vs O2 vs air, 5 x O2 vs air	Mod BORG, VAS, numerical scale	Failed to improve dyspnoea except in hypoxic patients	
2-	Currow[39]	2009	Cancer patients, respiratory and cardiac disease	413	Consecutive cohort study	Face-to-face assessments pre and post home oxygen	0-10 numerical scale	Non-significant improvement in dyspnoea in 150 patients	
1+	Abernethy[40]	2010	Various diagnoses with breathlessness, PaO2>7.3	239	Multi-centre, double-blind, RCT	LTOT vs room air , 15 hours/day for 7 days	Numerical scale 0-10, functional impact, anxiety, McGill QoL Questionnaire, drowsiness, nasal irritation	No difference between the groups.	

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

Level	First author	Year	Subjects	N	Design	Intervention	Evaluation	Results	
1-	Viola[73]	2008	Advanced cancer patients	n/a	Systematic literature review	4 drug classes inc. corticosteroids	No controlled trials identified		
3	Elsayem[47]	2007	Cancer with upper airway obstruction	3	Case series	IV dex 10mg 6 hourly; IV methylprednisolone 125mg 6hourly; IV dex 10mg 6 hourly	0-10 score in 2 cases Clinical assessment in 1 case	Scores 8-10/10 reduced to 1-2/10 within 12 hrs. Clinical resolution of stridor in final case.	
3	Hardy[74]	2001	Advanced malignant disease	15	Prospective survey		Clinical assessment of response	5/13 better; 6/13 no change; 2/13 worse	

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

	First author*	Year	Subjects	N	Design	Intervention	Evaluation	Results	
3	Ahmedazai[48]	1988	Case study	1	Case study	Nabilone 0.5mg 12 hrly	Clinical	Breathlessness and anxiety improved	
3	Maida[49]	2008	Palliative care patients with cancer	112	Prospective observational study	Nabilone 0.5-1mg initially, average dose at end 1.79mg	ESAS	No significant improvement in breathlessness ratin	

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

Level	First author*	Year	Subjects	N	Design	Intervention	Evaluation	Results	
1-	Poole[55]	1998	Severe COPD	18	Randomised, double blind, crossover	Nebulised **saline** vs nebulised terbutaline	FEV1, FVC, Breathlessness on Likert scale and VAS	Breathlessness improved in both groups, but more i terbutaline group (thought to relate to inc. FEV1)	
1-	Khan[56]	2004	COPD patients	34	Single blind, randomised, placebo controlled (N=6 crossover)	Nebulised **saline** via efficient nebuliser vs inefficient nebuliser	FEV1, FVC, breathlessness (7 point Likert scale), benefit score (7 point scale)	Statistically significant improvement in breathlessne in active group without bronchodilator effect	
3	Shimoyama[50]	2002	Terminal stage cancer with breathlessness	3	Case series	Neb **furosemide** 20mg QDS	VAS	VAS reduced by 5-9 points, sustained effect fo 2 weeks	

1-	Stone[51]	2002	Terminal stage cancer with breathlessness	7	Pilot RCT - Double blind, randomized, placebo controlled, cross over	Neb **furosemid**e vs saline	VAS	Trend to worsening VAS, not statistically sig. Pilot finished early	
3	Kohara[75]	2003	Cancer patients with breathlessness	15	Uncontrolled, open study	Neb **furosemide** 20mg	Cancer dyspnoea scale 0min and 60 min	12 patients reported reduced anxiety and effor to breath	
1-	Ong[52]	2004	Moderate-severe COPD	19	Double blind, randomised, crossover	Neb **furosemide** 40mg vs saline	VAS during exercise – incremental and constant rate	VAS lower with furosemide – stat sig with constant rate exercise	
1-	Wilcock[53]	2008	Primary/secondary Lung cancer with breathlessness	15	Double blind, randomised, placebo controlled	Neb **furosemide** 40mg vs saline vs no treatment	Dyspnoea rating scale, number reading test, arm exercise	No difference between arms	
2-	Wilcock[54]	1994	Cancer with breathlessness	6	Unblinded, cross over	Neb saline vs low dose **lignocaine** vs higher dose lignocaine	VAS o,10, 20, 30 & 60 mins	VAS reduced after all treatments. Distress of breathing increased with lignocaine	

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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Field Code Changed

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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 Bolean 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 terminal*.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

Keeley PW. Clinical Guidelines. *Palliative Medicine* 2003; **17:** pp. 368-374