Pharmacological management of dyspnoea

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Purpose of review

This paper reviews the current evidence for the pharmacological treatment of refractory symptomatic breathlessness in people with advanced life-limiting illnesses. The paper does not explore changes in function.

Recent findings

Oral and parenteral opioids reduce dyspnoea, and data continue to add to this indication for these drugs. Optimal dosing of opioids is being refined. Interest in other medications continues to be explored – benzodiazepines, nebulised frusemide, and selective serotonin reuptake inhibitors – but their role in day-to-day clinical practice is not defined.

Summary

Low-dose regular opioids, especially sustained-release preparations, have a key role in the pharmacological management of dyspnoea when titrated for effect, and may be used regularly across a range of underlying pathophysiologies. Key research questions for all the current symptomatic pharmacological agents used in refractory dyspnoea remain.

Keywords

drug therapy, dyspnoea, evidence-based medicine, palliative care

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Abbreviations

COPD	chronic obstructive pulmonary disease
FEV_1	1 s forced expiratory volume
VAS	visual analogue scale

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Introduction

Breathlessness is a frightening symptom that is frequently associated with life-limiting illnesses. Refractory breathlessness refers to continuing dyspnoea even when the underlying reversible components of breathlessness have been optimally treated. Unlike many other symptoms, breathlessness tends to worsen as death approaches. Breathlessness has a significant impact on both the person with the life-limiting illness and his/her caregiver(s).

Although there have been many attempts to link the sensation of breathlessness with descriptors and underlying pathophysiology, to date this work has not generated conclusions that can be linked with specific pharmacological interventions [1,2]. As such, this review covers breathlessness irrespective of the underlying causes of the symptom.

Much work has been done to explore both improved function and relief of the psychosomatic experience of breathlessness. This review discusses the symptomatic relief of breathlessness only, and does not review changes in functional status.

There are several classes of medications used for the symptomatic treatment of dyspnoea. As this is the first review in this series, it will focus on recent papers, but will also refer to earlier work that underpins key recommendations or current research directions.

Over the past 30 years, there have been many attempts to look at medications that may consistently help to reduce the sensation of breathlessness for people in whom the cause can no longer be modified. Of these agents, the most promising are still the opioids, but there are data on a number of classes of medications, including benzodiazepines, inhaled frusemide and selective serotonin reuptake inhibitors, to support further prospective studies. Other agents that, at this time, do not warrant further study currently include methylxanthines [3–5], antipsychotics [6], antihistamines [7–9], inhaled local anaesthetics [10,11] and nonsteroidal anti-inflammatory drugs [12].

Opioids

The definitive review of the role of opioids by Jennings *et al.* [13] was published in 2002 and covered the literature up to May 1999. This study was a meta-analysis of existing studies, none of which was adequately powered

to confirm and quantify the benefits of using opioids. The study included all randomised double-blind placebo-controlled studies that could be identified in the English literature in which the aim of administering opioids was reducing breathlessness. Administration of the medication was separated into oral or parenteral, or nebulised routes of administration. The populations studied were heterogeneous in underlying pathology and performance status, but shared similar levels of breathlessness at baseline.

Across the studies, oral and parenteral administration of opioids demonstrated a statistically significant and clinically consistent improvement in the symptom of breathlessness. The magnitude of this benefit was an absolute improvement of 7 mm on a 100 mm visual analogue scale (VAS), which translates to approximately 16% improvement over baseline levels of dyspnoea. A sub-group analysis of only people with chronic obstructive pulmonary disease (COPD) showed similar direction and magnitude of benefit.

As with all systematic reviews, the conclusions are limited by the source data available at the time the study was done. Importantly, the data for dose were unable to inform routine clinical practice given the variations in trial design.

At the same time as the systematic review was being prepared, a single-site double-blind placebo-controlled crossover randomised controlled study [14] was being conducted using a single morning dose of 20 mg of sustained-release morphine for 4 days. Thirty eight opioid-naïve patients had complete data, with 88% of these people having COPD, and the balance mainly having cancer. More than 70% had an Eastern Cooperative Oncology Group performance status score of *2* or more, and 71% were using long-term oxygen at home. Day 4 and day 8 morning and evening VAS scores were the primary outcome. Morphine improved breathlessness in this population in both the morning and evening. The magnitude of benefit was similar to that found in the paper by Jennings *et al.* [13], with a peak mean benefit of 9.5 mm on a 100 mm VAS or a net benefit over baseline of approximately 19%.

A secondary analysis of this paper did not demonstrate a relationship between baseline dyspnoea and response to opioids, in contrast to earlier work in the area [15,16]. In this exploratory study, no relationship was defined between response to opioids and baseline dyspnoea (Spearman's rank correlation coefficient = 0.03, $P = 0.88$). The study was not powered to define predictors of response, but younger, more active people and those with cardiac dysfunction as the primary cause of their breathlessness should be studied in greater detail. This latter group appeared to have a significant response to opioids in another key study [17]. Although labelled as a pilot study, Johnson and colleagues [17] demonstrated a 23 mm reduction in median breathlessness ($P = 0.022$) in a group of people with New York Heart Association grade III or IV heart failure treated with 5 mg of immediate release morphine sulphate solution orally every 6 h for 4 days in a randomised double-blind placebo-controlled crossover study. Initial sedation was experienced in the opioid arm, to which the participants became tolerant in the first 48 h of treatment.

A more recent paper [18••] has explored the role of epidural methadone in a population of nine people older than 60 years with severe refractory breathlessness as a result of severe COPD with a mean 1 s forced expiratory volume (FEV_1) of 25% of normal. In this single-group study, 6 mg/24 h of open-label epidural methadone was infused at the T4–T5 level for at least 1 month; complete data were obtained for seven people. At 1 month, rating of breathlessness using the transitional dyspnoea index was significantly better compared with the end of the first week (approximately 5.3 points on a 19-point scale; $P < 0.05$). Similarly, the breathlessness rating on the transitional dyspnoea index was better at the end of the first week compared with baseline (approximately 3.8 points on a 19-point scale; $P < 0.01$). The dyspnoea subscale of the Chronic Respiratory Diseases Questionnaire improved to 4.6 from a mean of 2.4 on a 0–10 scale ($P < 0.05$) in the month of observed treatment. Two patients had to be withdrawn because of line infection or migration during the month, but there was no evidence of functional respiratory problems in any participant. Although promising, more work needs to be done to understand the magnitude of the benefit in blinded studies that also include people with causes of breathlessness other than COPD. Whether the level at which the methadone was infused is clinically meaningful remains to be determined.

Although widely used, nebulised opioids have not demonstrated a consistent benefit in relieving refractory dyspnoea, as summarised in the systematic review by Jennings *et al* [13]. In the results of this systematic review, there was not even a trend for nebulised opioids to suggest that a more adequately powered study is likely to yield clinically significant benefits across the population in question. Three more recent systematic reviews [19,20•,21•] came to similar conclusions; there have been several small studies that have been unable to define a uniform benefit for nebulised opioids. Factors that may account for small variations in the perceived response to opioids include the particle size developed by the nebuliser and the dose administered, as evidenced by the use of inhalational systems that do predictably deliver systemic opioids such as morphine [22].

Small randomised studies continue to be done on nebulised opioids [23]. Given the demonstrated benefit of parenteral morphine in reducing dyspnoea, the definitive study design is to compare oral or parenteral opioids with nebulised opioids in the palliative care patient population. A pilot study [24•] has explored this in a double-blind placebo-controlled crossover trial. An adequately powered study is warranted.

Concerns continue to be expressed about the safety of opioids in this patient population [25–27]. There are limited prospective safety data in the palliative population, and more work needs to be done. Although studies do measure physiological parameters in people being introduced to opioids for dyspnoea, none of these studies is powered to be a true safety study [28,29•]. In the study by Allen *et al.* [29•], for example, a single dose of diamorphine is administered, but the physiological measures are taken before peak plasma opioid metabolite levels may be reached from a single dose. Good short- and long-term safety studies of regular opioids in people with end-stage disease, especially COPD, are required, where toxicity is measured prospectively in the palliative population with steady-state dosing [30,31].

Optimal dosing from all these studies has not been defined. Importantly, only two studies [16,32] try to address the opioid dose for people already established with opioids. This is an area where more work is needed urgently.

Are all opioids or their metabolites the same? This is still to be determined. Modest studies have included morphine-6-glucuronide [33], dihydrocodeine [34–36], codeine [7], fentanyl [37] and diamorphine [29•,38,39]. Transmucosal, transdermal, and nebulised fentanyl is being evaluated [40,41], but studies are small and uncontrolled. Each of these opioids' respective roles for the clinician at the bedside is yet to be determined in equivalence studies with morphine as the best practice comparator.

Benzodiazepines

Despite widespread use, the role of benzodiazepines in helping to ameliorate refractory dyspnoea is poorly defined in the population of people accessing supportive or palliative care. There have been a number of underpowered studies on benzodiazepines including alprazolam [42,43] and diazepam [9,44,45]. None of these studies is adequately powered to define the role in the short term compared with placebo or opioids; their contribution to the literature is to define the likely magnitude of benefits and measurement tools for future definitive studies.

A recent paper focused specifically on the terminal stage of care for people with shortness of breath [46]. In this three-group single-blind study, people with severe dyspnoea (average 7/10 on a Borg scale where 10 = worst possible dyspnoea) in what was expected to be their last week of life were offered regular 4 hourly subcutaneous morphine and subcutaneous midazolam rescue; regular 4 hourly midazolam with morphine rescue; or regular 4 hourly doses of both regimens. If the patients were opioid-naïve each morphine dose was 2.5 mg, and if they were not naïve to opioids a 25% increase from baseline was administered. Midazolam 5 mg was administered at each dose interval irrespective of previous benzodiazepine exposure. Dyspnoea was measured on an 11-point Borg scale at 24 h and 48 h. All three groups experienced significant reductions in dyspnoea at both time points. The group who were receiving regular midazolam with morphine breakthrough doses had the highest levels of unrelieved dyspnoea at 48 h. Cognition, level of interaction and anxiety (the latter had baseline levels reported) were not reported during the study. Twenty one patients were dead at 24 h, and another 10 patients at 48 h. The fact that regular benzodiazepine alone had the poorest level of dyspnoea relief, the assumption that adding an anxiolytic may be a key benefit without anxiety being prospectively reported, and the relatively large doses (in combination) offered to opioid- and benzodiazepine-naïve patients limit the ability to generalise these results widely to clinical practice.

Frusemide

The role of nebulised frusemide has continued to attract broad interest in respiratory medicine over the past two decades [47]. The distinction between changing the underlying pathophysiology of breathlessness and treating an established symptom is an important one. Refractory dyspnoea is, by definition, intractable because the underlying reversible causes of dyspnoea have been adequately but successfully addressed clinically. From preclinical and clinical data, the mode of action of nebulised frusemide in reducing the sensation of breathlessness is not clear in the supportive and palliative care population. There are data to suggest that frusemide acts on airway mechanoreceptors [48] and that this process may be mediated by the vagus nerve. Inhaled frusemide also appears to protect from bronchospasm in experimental conditions for people with known precipitants for asthma [49–51].

The sensation of breathlessness can be improved in laboratory-induced dyspnoea in healthy subjects using nebulised frusemide. In a double-blind placebo-controlled crossover study, inhaled frusemide did not affect the CO_2 response curve from experimentally increased levels of P_aco_2, but on a 200 mm VAS, scores were significantly reduced after frusemide administration when compared with baseline. What was not reported

were the postintervention differences between placebo and frusemide [52].

A study by Ong and colleagues [53] explored dyspnoea in 19 people with moderate or severe COPD [mean percentage of predicted FEV_1 of 42% (range, 19–69%)] and Medical Research Council Scale breathlessness grade 4 or 5 by comparing exercise ability after either placebo or inhaled frusemide (40 mg) in a double-blind crossover trial. On a 100 mm VAS measured after incremental and constant work rate exercise, dyspnoea was reduced after nebulised frusemide. It should be noted that there was a statistically significant increase in FEV_1 after frusemide alone compared with placebo (1.05 l increased to 1.10 l; $P < 0.05$). This supports other studies suggesting that there is a specific bronchodilator effect of nebulised frusemide. As such, the definitive study in the supportive and palliative care population is still awaited, to answer the question: do people have less breathlessness after inhaled frusemide when they have no evidence of bronchoconstriction, and no improvement in FEV, after nebulised frusemide?

In the supportive and palliative care population, the evidence for clinical practice is again limited, comprising only case series and small pilot studies [54,55]. The largest study in this population compared breathlessness scores before and after 20 mg nebulised frusemide using the Japanese version of the Cancer Dyspnoea Scale. Twelve of 15 patients had lower dyspnoea scores after the intervention ($P = 0.007$). Even if this result were discounted by a sizeable placebo effect, it supports further study. Reduction in both anxiety and the perceived work of breathing were also reported as significant outcomes. There are enough indications therefore to suggest that further work on nebulised frusemide in rigorously designed, blinded and randomised studies would define the true response in people at the end of life with dyspnoea and *no* component of reversible airways disease.

Selective serotonin reuptake inhibitors

Anxiety is an understandable component of breathlessness, in both the acute and chronic setting. Treating diagnosed anxiety appears to have a place in the care of people with refractory dyspnoea [56], using agents such as buspirone and nortriptyline [56–60].

The concept that a selective serotonin reuptake inhibitor may have some demonstrable benefit would fit with the broader indications for this class of medications. There are two brief case series of people with mild to severe COPD in the literature [61,62], one with people who meet mood disorder or anxiety criteria, and another with a sub-cohort who do not meet such criteria when assessed by a psychiatrist. At a mechanistic level, serotonergic modulation of breathing and its sensation may be a target for such therapy. This may be modulated by CO_2 sensitivity [62]. Although these are open-label case series, both report people for whom dyspnoea was reduced weeks to months after sertraline was started and other factors appeared stable.

Conclusion

In aggregate, evidence generated by a number of brief intervention efficacy studies and systematic reviews, there is evidence to support the safe use of opioids in people with refractory dyspnoea. Steady-state use, especially employing sustained release preparations, is best. There are emerging data of patient populations that may derive the most benefit from these symptomatic interventions.

Considering opioids, where there is the best evidence of efficacy, there are still few data to inform practice in key areas. The following categories of study are necessary to firmly establish the role of opioids in the care of palliative patients with dyspnoea.

(1) effectiveness studies (to determine how the efficacy studies translate into the world of every day clinical practice);
(2) dose-ranging studies (to establish a dose–response relationship, to establish optimal doses in people who are opioid naïve, and to define dose increments for people already taking opioids);
(3) long-term effectiveness studies (to see if the short-term benefits of medications efficacy are maintained);
(4) proper blinded comparisons between different opioids; and
(5) safety studies (where the study is powered to adverse outcomes such as respiratory depression in opioid use, rather than to benefit of reduced breathlessness).

Similar studies will subsequently need to be done to test the other agents currently being administered to reduce breathlessness in people with refractory dyspnoea in the setting of supportive or palliative care.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 140–141).

1 Simon PM, Schwartzstein RM, Weiss JW, *et al.* Distinguishable types of dyspnea in patients with shortness of breath. Am Rev Respir Dis 1990; 142:1009–1014.

2 Harver A, Mahler DA, Schwartzstein RM, Baird JC. Descriptors of breathlessness in healthy individuals: distinct and separable constructs. Chest 2000; 118:679–690.

3 Mahler DA, Matthay RA, Snyder PE, *et al.* Sustained release theophylline reduces dyspnoea in nonreversible obstructive airway disease. Am Rev Resp Dis 1985; 131:22–25.

4 McKay SE, Howie CA, Thomson AH, *et al.* Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. Thorax 1993; 48:227–232.

5 Murciano D, Auclair MH, Pariente R, Aubier M. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. N Engl J Med 1989; 320:1521–1525.

6 O'Neill PA, Morton PB, Stark RD. Chlorpromazine — a specific effect on breathlessness? Br J Clin Pharmacol 1985; 19:793–797.

7 Rice KL, Kronenberg RS, Hedemark LL, Niewoehner DE. Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction. Br J Dis Chest 1987; 81:287–292.

8 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; 109:975–981.

9 Woodcock AA, Gross ER, Geddes DM. Drug treatment of breathlessness: contrasting effects of diazepam and promethazine in pink puffers. Br Med J (Clin Res Ed) 1981; 283:343–346.

10 Stark RD, O'Neill PA, Russell NJ, *et al.* Effects of small particle aerosols of local anaesthetic on dyspnoea in patients with respiratory disease. Clin Sci (Lond) 1985; 69:29–36.

11 Hamilton RD, Winning AJ, Perry A, Guz A. Aerosol anesthesia increases hypercapnic ventilation and breathlessness in laryngectomized humans. J Appl Physiol 1987; 63:2286–2292.

12 Schiffman GL, Stansbury DW, Fischer CE, *et al.* Indomethacin and perception of dyspnea in chronic airflow obstruction. Am Rev Respir Dis 1988; 137:1094–1098.

13 Jennings AL, Davies AN, Higgins JP, *et al.* A systematic review of the use of opioids in the management of dyspnoea. Thorax 2002; 57:939–944.

14 Abernethy AP, Currow DC, Frith P, *et al.* Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ 2003; 327:523–528.

15 Currow DC, Abernethy AP, Plummer J, Frith P. Can we predict which patients with refractory dyspnea will respond to opioids? J Pall Med (in press)

16 Allard P, Lamontagne C, Bernard P, Tremblay C. How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial. J Pain Symptom Manage 1999; 17:256–265.

17 Johnson MJ, McDonagh TA, Harkness A, *et al.* Morphine for the relief of breathlessness in patients with chronic heart failure – a pilot study. Eur J Heart Fail 2002; 4:753–756.

18 •• Juan G, Ramón M, Valia JC, *et al.* Palliative treatment of dyspnea with epidural methadone in advanced emphysema. Chest 2005; 128:3322–3328.
This is a small but important study that includes both short- and long-term follow-up of thoracic level epidural morphine in a case series, but shows potential for further study.

19 Foral PA, Malesker MA, Huerta G, Hilleman DE. Nebulized opioids use in COPD. Chest 2004; 125:691–694.

20 • Brown SJ, Eichner SF, Jones JR. Nebulized morphine for relief of dyspnea due to chronic lung disease. Ann Pharmacother 2005; 39:1088–1092.
This is a thorough systematic review that has been done by pharmacists, and again concludes that nebulised opioids do not predictably reduce refractory dyspnoea when compared to placebo.

21 • Polosa R, Simidchiev A, Walters EH. Nebulised morphine for severe interstitial lung disease. Cochrane Database of Systematic Reviews 2007. Art. No.: CD002872. DOI: 10.1002/14651858.CD002872.
This systematic review could only define one paper in this sub-population of people with dyspnoea. Nebulised morphine was again not shown to deliver benefit.

22 Ward ME, Woodhouse A, Mather LE, *et al.* Morphine pharmacokinetics after pulmonary administration from a novel aerosol delivery system. Clin Pharmacol Ther 1997; 62:596–609.

23 Grimbert D, Lubin O, de Monte M, *et al.* Dyspnea and morphine aerosols in the palliative care of lung cancer. Rev Mal Respir 2004; 21 (6 Pt 1):1091–1097.

24 • Bruera E, Sala R, Spruyt O, *et al.* Nebulized versus subcutaneous morphine for patients with cancer dyspnea: a preliminary study. J Pain Symptom Manage 2005; 29:613–618.
This study describes the methodology that should be used in the definitive study to compare the role of nebulised opioids against the current best practice delivery of opioids for refractory dyspnoea – morphine orally or parenterally.

25 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; 157:1877–1880.

26 Berrill JW, Linnasne SJ. Morphine for management of refractory dyspnoea: opiates should be used with caution. Br Med J 2003; 327:1288–1289.

27 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006. Executive Summary. 2006. http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=996? Accessed 29 June 2007.

28 Mazzocato C, Buclin T, Rapin CH. The effects of morphine on dyspnea and ventilatory function in elderly patients with advanced cancer: a randomized double-blind controlled trial. Ann Oncol 1999; 10:1511–1514.

29 • Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. Palliat Med 2005; 19:128–130.
This is a small open-label series that seeks to define acute toxicity from opioids in elderly people. This is a single-dose study of a subcutaneously administered dose of diamorphine.

30 Stuart-Harris R, Joel SP, McDonald P, *et al.* The pharmacokinetics of morphine and morphine glucuronide metabolites after subcutaneous bolus injection and subcutaneous infusion of morphine. Br J Clin Pharmacol 2000; 49:207–214.

31 Currow D, Abernethy A, Frith P. Morphine for management of refractory dyspnoea. BMJ 2003; 327:1288–1289. (letter).

32 Bruera E, MacEachern T, Ripamonti C, Hanson J. Subcutaneous morphine for dyspnea in cancer patients. Ann Intern Med 1993; 119:906–907.

33 Quigley C, Joel S, Patel N, *et al.* A phase I/II study of nebulized morphine-6-glucuronide in patients with cancer-related breathlessness. J Pain Symptom Manage 2002; 23:7–9.

34 Woodcock AA, Gross ER, Gellert A, *et al.* Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. N Engl J Med 1981; 305:1611–1616.

35 Johnson MA, Woodcock AA, Geddes DM. Dihydrocodeine for breathlessness in 'pink puffers'. Br Med J 1983; 286:675–677.

36 Chua TP, Harrington D, Ponikowski P, *et al.* Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol 1997; 29:147–152.

37 Coyne PJ, Viswanathan R, Smith TJ. Nebulized fentanyl citrate improves patients' perception of breathing, respiratory rate, and oxygen saturation in dyspnea. J Pain Symptom Manage 2002; 23:157–160.

38 Eiser N, Denman WT, West C, Luce P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the 'pink puffer' syndrome. Eur Respir J 1991; 4:926–931.

39 Williams SG, Wright DJ, Marshall P, *et al.* Safety and potential benefits of low dose diamorphine during exercise in patients with chronic heart failure. Heart 2003; 89:1085–1086.

40 Benitez-Rosario MA, Martin AS, Feria M. Oral transmucosal fentanyl citrate in the management of dyspnea crises in cancer patients. J Pain Symptom Manage 2005; 30:395–397.

41 Shirk MB, Donahue KR, Shirvani J. Unlabeled uses of nebulized medications. Am J Health Syst Pharm 2006; 63:1704–1716.

42 Greene JG, Pucino F, Carlson JD, *et al.* Effects of alprazolam on respiratory drive, anxiety, and dyspnea in chronic airflow obstruction: a case study. Pharmacotherapy 1989; 9:34–38.

43 Man GC, Hsu K, Sproule BJ. Effect of alprazolam on exercise and dyspnea in patients with chronic obstructive pulmonary disease. Chest 1986; 90:832–836.

44 Mitchell-Heggs P, Murphy K, Minty K, *et al.* Diazepam in the treatment of dyspnoea in the 'Pink Puffer' syndrome. Q J Med 1980; 49:9–20.

45 Sen D, Jones G, Leggat PO. The response of the breathless patient treated with diazepam. Br J Clin Pract 1983; 37:232–233.

46 Navigante AH, Cerchietti LC, Castro MA, *et al.* Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. J Pain Symptom Manage 2006; 31:38–47.

47 Robuschi M, Gambaro G, Spagnotto S, *et al.* Inhaled frusemide is highly effective in preventing ultrasonically nebulised water bronchoconstriction. Pulm Pharmacol 1989; 1:187–191.

48 Nishino T, Ide T, Sudo T, Sato J. Inhaled furosemide greatly alleviates the sensation of experimentally induced dyspnea. Am J Respir Crit Care Med 2000; 161:1963–1967.

49 Bianco S, Pieroni MG, Refini RM, *et al.* Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. N Engl J Med 1989; 321:1069–1073.

50 Bianco S, Vaghi A, Robuschi M, Pasargiklian M. Prevention of exercise-induced bronchoconstriction by inhaled frusemide. Lancet 1988; 2:252–255.

51 Prandota J. Furosemide: progress in understanding its diuretic, anti-inflammatory, and bronchodilating mechanism of action, and use in the treatment of respiratory tract diseases. Am J Ther 2002; 9:317–328.

52 Minowa Y, Ide T, Nishino T. Effects of inhaled furosemide on CO(2) ventilatory responsiveness in humans. Pulm Pharmacol Ther 2002; 15:363–368.

53 Ong KC, Kor AC, Chong WF, *et al.* Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 169:1028–1033.

54 Shimoyama N, Shimoyama M. Nebulized furosemide as a novel treatment for dyspnea in terminal cancer patients. J Pain Symptom Manage 2002; 23:73–76.

55 Stone P, Rix E, Kurowska A, Tookman A. Re: nebulized furosemide for dyspnea in terminal cancer patients. J Pain Symptom Manage 2002; 24:274–275.

56 Brenes GA. Anxiety and chronic obstructive pulmonary disease: prevalence, impact and, treatment. Psychosom Med 2003; 65:963–970.

57 Argyropoulou P, Patakas D, Koukou A, *et al.* Buspirone effect on breathlessness and exercise performance in patients with chronic obstructive pulmonary disease. Respiration 1993; 60:216–220.

58 Garner SJ, Eldridge FL, Wagner PG, Dowell RT. Buspirone, an anxiolytic drug that stimulates respiration. Am Rev Respir Dis 1989; 139:946–950.

59 Mendelson WB, Martin JV, Rapoport DM. Effects of buspirone on sleep and respiration. Am Rev Respir Dis 1990; 141:1527–1530.

60 Singh NP, Despars JA, Stansbury DW, *et al.* Effects of buspirone on anxiety levels and exercise tolerance in patients with chronic airflow obstruction and mild anxiety. Chest 1993; 103:800–804.

61 Papp LA, Weiss JR, Greenberg HE, *et al.* Sertraline for chronic obstructive pulmonary disease and comorbid anxiety and mood disorders. Am J Psychiatry 1995; 152:1531.

62 Smoller JW, Pollack MH, Systrom D, Kradin RL. Sertraline effects on dyspnea in patients with obstructive airways disease. Psychosomatics 1998; 39:24–29.