EPEC-O

Education in **P**alliative and **E**nd-of-life **C**are - **O**ncology

Participant's Handbook

Module 3j:
Symptoms – Dyspnea

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Case*

M.B. is a 55-year-old longshoreman with a long history of smoking with inoperable stage IIIb non-small cell lung cancer and chronic obstructive pulmonary disease. He notes dyspnea that has worsened over the past 3 months. He uses oxygen at 2 liters per nasal canula. He is often anxious.

* This case is not on an EPEC-O Curriculum trigger tape.

Introduction

Dyspnea is *the uncomfortable sensation or awareness of breathing or needing to breathe, i.e., shortness of breath*. Possible specific underlying causes of dyspnea are many. Physical etiologies include airway obstruction, bronchospasm, hypoxemia, pleural effusion, pneumonia, pulmonary edema, pulmonary embolism, thick secretions, anemia, and metabolic derangement. Psychological, social, and spiritual issues, such as loss and grief or fear of dying can cause anxiety. Anxiety can cause dyspnea.

Prevalence

Prevalence of dyspnea among cancer patients has been reported to be between 21-90%, depending on the type and stage of cancer.[1,2,3] It is particularly common in patients with primary or metastatic involvement of the lung. However, it is also reported by patients with no direct lung involvement. Dyspnea may also be due to other concurrent cardiopulmonary problems, such as chronic obstructive pulmonary disease and congestive heart failure in the patient with cancer.

Prognosis

Dyspnea is associated with a poor prognosis. If there is no effective treatment for the underlying malignancy, prognosis is less than 6 months.

Pathophysiology

The pathophysiology of dyspnea is multifactorial and incompletely understood (see Figure 1).[4,5,6] The respiratory center in the medulla and pons coordinates the activity of the diaphragm, the intercostal muscles, and accessory muscles of respiration. It receives sensory information from central and peripheral chemoreceptors, peripheral

Figure 1: Schematic representation of the control of respiration

From: Thomas JR, von Gunten CF. Clinical management of dyspnea. *Lancet Oncol.* 2002;3(4):223-228. PMID: 12067684.
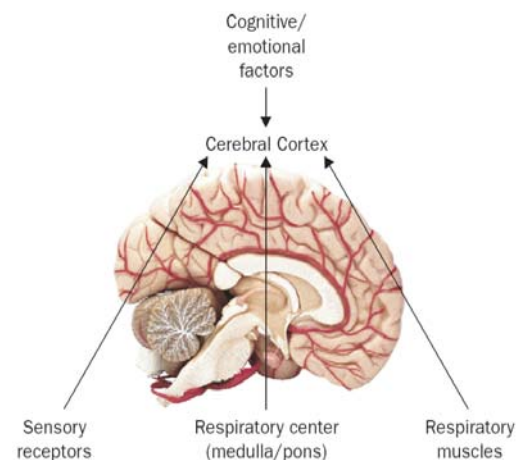
mechanoreceptors from muscles, tendons, and joints, and pulmonary vagal afferents. These vagal afferents include pulmonary stretch receptors that are activated by lung inflation, pulmonary irritant receptors triggered by air flow and smooth muscle tone, and alveolar C fibers that respond to pulmonary interstitial and capillary pressure. These afferents may also send information directly to the cerebral cortex. It is believed the cerebral cortex integrates this sensory input with other cognitive and emotional factors as well as motor information from the respiratory center.[7,8]

Three concepts have emerged to explain the pathophysiology and guide therapy: 1) work of breathing, 2) chemical effects, and 3) neuromechanical dissociation.

Work of breathing

Most studies point to increased respiratory work as an important component of dyspnea. The effort required for breathing against increased resistance in chronic obstructive pulmonary disease or bronchial obstruction, or breathing with weakened muscles in cachexia, is sensed as dyspnea.[4]

Chemical effects

Most patients with cancer and dyspnea are not hypoxemic. Medullary chemoreceptors sense hypercapnia while carotid and aortic body chemoreceptors sense hypoxemia. Stimulation of these chemoreceptors can cause dyspnea independent of carbon dioxide or oxyten levels.[9,10] It takes moderately severe levels of hypoxemia to trigger the peripheral chemoreceptors.[11] In addition, the compensatory increase in ventilation triggered by hypoxemia drives down the carbon dioxide level, which then partially negates the effect of the hypoxemia.

Neuro-mechanical dissociation

Dyspnea occurs when there is a mismatch between what the brain desires for respiration and the sensory feedback it receives.[12] For example, when researchers limit the inspiratory flow rate at which a subject is allowed to breathe, dyspnea results despite no change in respiratory work or chemical status.[13]

Assessment

The 'gold standard' for diagnosis of dyspnea is patient self-report.

There are no other reliable, objective measures of dyspnea. Respiratory rate, oxygen saturation, and arterial blood gas determinations do not correlate with, nor measure dyspnea. Patients may be hypoxemic but not dyspneic or dyspneic but not hypoxemic.

The severity scales developed for pain (numerical, visual analogue scale) have been reliably used to assess dyspnea.

In addition to taking a history appropriate for the patient's situation, a physical examination may provide confirmatory information. Objective signs may include areas of

pulmonary dullness, crackles, inability to clear secretions, stridor, bronchospasm (wheezing), cyanosis (central or peripheral), intercostals indrawing, and tachypnea.

Simple studies such as pulse oximetry, complete blood count and a chest X-ray are most often sufficient to clarify an understanding of the pertinent pathophysiology. When the possible benefits of further investigation exceed the burdens, additional studies may be warranted.

Management

The therapeutic goal of symptomatic management of dyspnea is to relieve the patient's sense of breathlessness. Specific therapy to manage underlying causes, eg, bronchodilators or stent placement to relieve focal obstruction, are appropriate in selected patients (see the appendix for strategies to manage selected causes).

To manage the experience of shortness of breath, both pharmacological and non-pharmacological interventions have been shown to be effective. Whatever the cause, elevating the head of the bed, keeping air moving using fans and open windows, and reducing environmental irritants are likely to be help. These strategies can be pursued simultaneously with strategies to manage the underlying causes.

Opioids

Opioids are the most effective medication for symptomatic control of dyspnea.[14,15,16] The mechanism by which opioids relieve dyspnea is not well understood. It is possible that opioids alter the perception of dyspnea in a manner analogous to their alteration of the perception of pain.

Opioids relieve dyspnea at doses far lower than those that depress the respiratory rate and oxygen saturation.

Opioid naïve patients

In opioid naïve patients, small amounts of morphine can relieve dyspnea.[17]

- Morphine, start with 10 – 15 mg PO q 1 h PRN or 5 mg SC q 30 min PRN. Titrate to effect using standard opioid dosing guidelines (see EPEC-O Module 2: Cancer Pain Management).

The duration of the effect is about 4 hours (consistent with the effective serum half-life of morphine and equivalent to that observed for pain relief).

For patients already using opioids

For patients on baseline opioids,

- Start by increasing the opioid dose by 25%, this often provides relief.[18] Titrate to effect using standard opioid dosing guidelines (see EPEC-O Module 2: Cancer Pain Management).

Chronic dyspnea

Once the chronic dyspnea is controlled, provide:

- An extended release formulation for baseline dyspnea control, and

- An immediate-release formulation of the same opioid for breakthrough dyspnea, eg, 10% of the total dose q 24 h, offered q 1 h PRN.

Nebulized opioids

Nebulized opioids have been reported to offer additional relief when given orally or parenterally in uncontrolled studies.[19] However, their use remains controversial. In small randomized controlled trials, nebulized water gave the same relief as nebulized morphine or hydromorphone.[20,21]

Anxiolytics

The role anxiety plays in dyspnea remains unclear. Patients frequently report anxiety concurrent with dyspnea. Dyspnea can lead to anxiety. Anxiety can exacerbate dyspnea. Opioids alone may break the cycle by relieving dyspnea, but they are not anxiolytic with sustained dosing.

Anxiolytics, eg, benzodiazepines, are frequently prescribed for anxiety related to dyspnea. However, when tested, the evidence for their effectiveness is not persuasive.[22,23,24,25] Anxiety itself may be responsible for only 10% of the sense of dyspnea. Therefore, do not use benzodiazepines alone as first line therapy for dyspnea. Benzodiazepines are also contraindicated in the frail or elderly as they may make short-term memory deficits worse.

Relief of dyspnea by other means such as opioids may be sufficient to remove the source of anxiety. However, treatment of anxiety does have a role in a subset of patients for whom anxiety is a prominent component of their distress. For these patients, a time-limited trial of benzodiazepines will demonstrate whether they are effective or not. They may be prescribed in conjunction with opioids without fear of respiratory depression when guidelines are followed.

- Lorazepam, start with 0.5 – 2.0 mg PO, SL, Buccal, or SC q 1 h PRN and titrate to effect. Once the total dose required in 24 hours has been established, provide 1/3 of the total dose q 8 h routinely.

Neuroleptics

Additionally, chlorpromazine, a major tranquilizer, and buspirone, a non-benzodiazepine anxiolytic have also been reported to decrease dyspnea.[26,27]

- Chlorpromazine, 10 – 25 mg PO q 6 h

- Buspirone, 15-30 mg daily (divided doses)

Oxygen

Oxygen can reverse hypoxemia. If hypoxemia is the cause of dyspnea, oxygen may be the only required therapy. However, its perceived benefit in patients with cancer who are dyspneic far exceeds the number who have hypoxemia.[28,29] There is likely a placebo effect of oxygen and the medical symbolism inherent in its administration. In addition, it has been observed that similar relief is experienced from cool air blowing on the face, eg, from a breeze or a fan. This may be explained by stimulation of the trigeminal nerve (V2 branch) having central inhibitory effects on dyspnea.[30,31,32] Thus, part of oxygen's effect may be due to this sensory stimulation rather than correction of hypoxemia or a pure placebo effect.

Many clinicians order oxygen therapy for dyspneic patients without considering the associated burdens or other therapeutic alternatives. It is costly and cumbersome, particularly when it is ordered for use in the patient's home. For many patients it dries their upper airway, unnecessarily restricts their mobility and alters their self-image, particularly if they are able to pursue their normal activities.

Cognitive/behavioral interventions

Dyspnea also has both cognitive and emotional components.[33] This has been well understood by pulmonary rehabilitation clinics for COPD.[34] Teaching breathing control, activity pacing, relaxation techniques, and psychosocial support are effective.

The demeanor of the clinician in the face of dyspnea is also important. A calm, confident demeanor can be reassuring to the patient and family and can help to diminish the anxiety component. By contrast, the clinician who responds to the frightened, anxious, dyspneic patient with a similar response is likely to have the opposite effect.

Refractory dyspnea

There may be a few patients with persistent severe dyspnea. In these rare cases, it is ethical to provide sedation in order to relieve the patient of her/his awareness of the symptom.[35] If therapeutic trials are not relieving dyspnea in a timely manner, consult a palliative medicine expert for assistance.

Dyspnea at the end-of-life

During the last hours of a person's life, there can be significant changes in a patient's breathing patterns, eg, Cheyne-Stokes breathing or short shallow respirations are cardinal signs that the patient is dying. Oxygen may prolong the dying process and it may not be appropriate. Focus on relieving the sense of shortness of breath, clearing or reducing secretions, and supporting everyone who is at the bedside (see EPEC-O Module 6: Last Hours of Living for details).

Bronchospasm

Although wheezes and/or rhonchi may be present, always look for intercostal retraction on examination (ie, evidence of bronchoconstriction, increased inspiratory pressures). If bronchospasm is suspected, a clinical trial of bronchospasmolytics may be indicated, although the potential of β-adrenergic agents (eg, albuterol) to cause adverse cardiac effects in patients with cardiac compromise must be carefully considered). Frail patients may have difficulties using inhalers, even with aerochambers. Nebulized aerosols may be more effective. If adequate doses are ineffective, discontinue therapy to minimize the number of medications, risk of adverse effects, and cost. Possible medications include:

- Steroids to reduce swelling and inflammation

- Dexamethasone, 2–20 mg PO, IV, SC daily (long half-life permits once-daily dosing; minimal mineralocorticoid effects and edema)

- Albuterol, 2–3 puffs q 4–8 h (with aerochamber), or albuterol 0.5%, 2.5–5.0 mg diluted to 4.0 ml with saline by nebulizer q 4 h

- Ipratropium bromide, 2–3 puffs q 4–8 h PRN or 0.125 mg q 4 h via nebulizer

- Theophylline and adrenergic agents may cause tremor and anxiety that will exacerbate dyspnea

Thick secretions

Thick secretions can accumulate around tracheostomy appliances and in airways of patients with obstruction or bronchospasm or those who are weak/frail. To minimize secretion buildup, maintain best possible hydration of the patient, keep mucous membranes moist, and increase humidity of inspired air (be careful not to increase risk of respiratory infections). If the cough reflex is strong, loosen secretions with nebulized saline and guaifenesin. If the cough reflex is weak, to dry secretions consider:

- Scopolamine, 0.1–0.4 mg SC, IV q 4 h or 1–3 transdermal patches q 72 h or 10–80 μg/h by continuous IV or SC infusion

- Glycopyrrolate, 0.4–1.0 mg daily by SC infusion or 0.2 mg SC, IV q 4–6 h PRN

- Hyoscyamine, 0.125 mg PO or SL q 8 h

Pleural effusion

See EPEC-O Module 3m: Malignant Pleural Effusions.

Anemia

Selected patients who are anemic and breathless may benefit from a blood transfusion. Consider a clinical trial. Transfuse to a hemoglobin level greater than10 g/dl and evaluate over several days. There may be an initial placebo effect. If the patient experiences a sustained increase in his or her energy and/or reduced breathlessness, consider following

the hematocrit and transfuse as needed. If there is no benefit, do not follow the hematocrit or repeat transfusion.

If the patient has a life expectancy of months or more, consider:

- Erythropoietin alfa 10,000 IU SC 3 times per week (onset of effect takes 4 weeks)

- Doubling the dose if the hemoglobin does not increase by more than 1 g/dl within 4 weeks. Darbepoetin weekly is an alternative.

Airway obstruction

Airway obstruction can cause considerable distress. High-pitched inspiratory stridor is often audible at a distance. Make sure tracheostomy appliances are cleaned regularly. If the patient is still eating and aspiration is likely, puree solids, thicken liquids with cornstarch or other thickeners, and instruct family members and caregivers on positioning during feeding and suctioning. Surgical management or radiation therapy may be appropriate. Other possible approaches include:

- Steroids to reduce swelling and inflammation
  - Dexamethasone, 2–20 mg PO, IV, SC daily (long half-life permits once-daily dosing; minimal mineralocorticoid effect or edema)
- Manage thick secretions
- Racemic epinephrine by inhaler
- Oxygen mixed with helium
- Stents in highly selected patients

Summary

Dyspnea is a significant clinical problem for cancer patients. Symptomatic management can be pursued concurrently with treatment directed at removing underlying causes.

Opioids are the first line therapy for symptomatic control of dyspnea. Although their mechanism of action is not entirely clear, when administered using standard dosing guidelines, they are safe and effectively relieve the symptom to the satisfaction of the majority of patients. Oxygen and benzodiazepines may be useful adjuncts. While respiratory depression has been an associated fear, there is no evidence that it is warranted. For refractory cases, sedation may be appropriate and ethical under the principle of double effect.

Key take-home points

1. Opioids relieve the distress of breathlessness in many patients without a measurable effect on their respiratory rate, hemoglobin saturation, or blood gas concentrations when dosing guidelines are followed.

2. Opioid treatment for dyspnea is consistent with good medical practice, and ethical when the intent is to relieve suffering. When dosing guidelines are followed it is exceedingly unlikely to cause drug abuse behaviors or premature death.

3. Benzodiazepines may relieve anxiety related to breathlessness.

4. Although oxygen is perceived as helpful by breathless patients, it is likely due to the placebo effect, local breeze, and the cooling of the skin around the nares as much as or more than the reversal of hypoxemia.

Pearls

1. Titrate opioids to the patient's report of relief; misadventures occur when titrating to the relief of onlookers like family or health care professionals.

2. In the United States, hospice programs can provide oxygen without demonstrating hypoxemia.

Pitfall

1. Don't titrate to respiratory rate—it is not a measure of breathlessness.

References

[1] Muers MF, Round CE. Palliation of symptoms in non-small cell lung cancer: a study by the Yorkshire Regional Cancer Organization Thoracic Group. *Thorax.* 1993;48:339-343. PMID: 7685550.

289 unselected patients were studied; 242 cases were confirmed histologically. Most symptoms inexorably worsened with time. The palliation index for haemoptysis was 86%, chest pain 73%, cough 34%, and breathlessness 30%; for systemic symptoms it was 54% for anorexia and 47% for malaise. Palliation was poor in many patients after surgery. Breathlessness was a particular problem in the group having best supportive care.

[2] Higginson I, McCarthy M. Measuring symptoms in terminal cancer: are pain and dyspnea controlled? *J R Soc Med.* 1989;82:264-67. PMID: 2474072.

The symptoms of 86 patients referred to a district terminal care support team were rated throughout care using a standardized schedule. 18 (21%) patients developed dyspnea as their main symptom, and this became the most severe symptom at death.

[3] Reuben DB, Mor V. Dyspnea in terminally ill cancer patients. *Chest.* 1986;89:234-236. PMID: 3943383.

The incidence of dyspnea was 70.2 percent, with prevalence rates generally exceeding 50 percent at any of three measurements. Underlying lung disease or cardiac and low performance on the Karnofsky scale were significantly associated with dyspnea. Lung, colorectal, and breast carcinomas were the most common cancers and accounted for almost 60 percent of dyspneic patients. In 23.9 percent, neither lung or pleural involvement nor underlying lung or heart disease could be identified as risk factors.

[4] Dudgeon DJ, Lertzman M. Dyspnea in the advanced cancer patient. *J Pain Symptom Manage.* 1998;16:212-219. PMID: 9803048. Full Text.

In 100 terminally ill cancer patients, the median VAS scores for shortness of breath and anxiety were 53 mm and 29 mm, respectively. Patients had a median of five different abnormalities that could have contributed to their shortness of breath. Only anxiety ($p = 0.001$), a history of smoking ($p = 0.02$), and

pCO2 levels were statistically significantly correlated with shortness of breath VAS scores. The potentially correctable causes of dyspnea included hypoxia (40%), anemia (20%), and bronchospasm (52%). The finding of very low MIPs suggests severe respiratory muscle weakness may contribute significantly to dyspnea in this patient population.

[5] Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. *N Engl J Med.* 1995;333:1547-1553. PMID: 7477171. Full Text.

[6] American Thoracic Society. Dyspnea: mechanisms, assessment, and management: a consensus statement. *Am J Respir Crit Care Med.* 1999;159:321-340. PMID: 9872857. Full Text.

[7] Peiffer C, Poline J, Thivard L, et al. Neural substrates for the perception of acutely induced dyspnea. *Am J Respir Crit Care Med.* 2001;163:951-957. PMID: 11282772. Full Text.

These authors performed a functional imaging study with positron emission tomography (PET) to assess brain activation in 8 healthy volunteers experiencing respiratory discomfort during loaded breathing. As compared with the unloaded control condition, high loaded breathing was associated with neural activation in three distinct brain regions, the right anterior insula, the cerebellar vermis, and the medial pons.

[8] Banzett RB, Mulnier HE, Murphy K, et al. Breathlessness in humans activates insular cortex. *Neuroreport.* 2000;11:2117-2120. PMID: 10923655.

PET scans revealed that air hunger activated the insular cortex in normal volunteers. The insula is a limbic structure also activated by visceral stimuli, temperature, taste, nausea and pain.

[9] Banzett RB, Lansing RW, Reid MB, et al: "Air hunger" arising from increased P_{CO_2} in mechanically ventilated quadriplegics. *Respir Physiol.* 1989;76:53-67. PMID: 2499025.

These authors gradually elevated inspired PCO2 in four tracheostomized quadriplegic subjects supported by constant mechanical ventilation. These subjects reported sensations of 'air hunger, eg, "short of breath" or "air-starved," when end-tidal PCO2 increased 10 Torr (mean) above their resting levels. These data suggest that changes in breathing are not necessary to evoke the sense of 'air hunger'.

[10] Lane R, Cockcroft A, Adams L, et al. Arterial oxygen saturation and breathlessness in patients with chronic obstructive airways disease. *Clin Sci.* 1987;72:693-698. PMID: 3595075.

Breathing supplemental oxygen produced a small fall in mean exercise ventilation and a large and consistent reduction in mean exercise breathlessness in 9 patients.

[11] Eyzaguirre C, Zapata P. Perspectives in carotid body research. *J Appl Physiol.* 1984;57:931-957. PMID: 6150019.

No single hypothesis has been proved beyond doubt. The multitude of biochemical and biophysical processes (some of them still unknown) operating at different receptor levels has made it very difficult to propose a unified mechanism of action.

[12] O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. *Am Rev Respir Dis.* 1993;148:1351-1357. PMID: 8239175.

23 patients with chronic airflow limitation had significantly ($p < 0.01$) higher levels of ventilation (% maximal voluntary ventilation) for a given work rate (slope of VE(%MVV)/WR(% pred max) = 1.51 +/- 0.18 versus 0.63 +/- 0.10; mean +/- SEM) and greater dynamic lung hyperinflation (DH) (change [delta] in end-expiratory lung volume [EELVdyn] = +0.31 +/- 0.11 L versus -0.16 +/- 0.22 L). Compared with normal subjects at a standardized VE (30 L/min), the CAL group was more breathless Borg = 4 +/- 1 versus 2 +/- 1, $p < 0.01$) and hyperinflated (EELVdyn = 75 +/- 3 versus 46 +/- 6% TLC, $p < 0.001$).

[13] Manning HL, Molinary EJ, Leiter JC. Effect of inspiratory flow rate on respiratory sensation and pattern of breathing. *Am J Respir Crit Care Med.* 1995;151:751-757. PMID: 7881666.

Subjects rated breathing discomfort on a visual analog scale while inspiratory flow rate was varied among four levels: 70%, 100%, 200%, and 300%. VAS ratings were significantly greater at the lowest and highest setting; there was no difference the middle range.

[14] 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. PMID: 6796885.

Dihydrocodeine reduced breathlessness by 20 per cent and increased exercise tolerance by 18 per cent. Oxygen also reduced breathlessness and provided additional benefit.

[15] Light RW, Muro JR, Sato RI, et al. Effects of oral morphine on breathlessness and exercise tolerance in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1989;139:126-133. PMID: 2492170.

Administration of opiates to 13 patients substantially increased the exercise capacity of patients. The improved exercise tolerance appears to be related to both a higher PaCO2 resulting in lowered ventilation requirements for a given workload and also to a reduced perception of breathlessness for a given level of ventilation.

[16] Bruera E, MacEachern T, Ripamonti C, et al. Subcutaneous morphine for dyspnea in cancer patients. *Ann Int Med*. 1993;119:906-907. PMID: 8215003. Full text

10 consecutive patients with terminal cancer, normal cognitive status, and shortness of breath receiving continuous oxygen via nasal prongs were treated with subcutaneous morphine or placebo in a cross-over design. A 50% decrease in dyspnea occurred in those treated with morphine without change in respiratory rate or oxygen saturation level.

[17] 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. PMID: 10643545.

Nine elderly patients with dyspnea due to lung involvement were randomized to receive either morphine subcutaneously (5 mg in seven opioid-naive patients and 3.75 mg in two patients on top of their regular oral dose of 7.5 mg q4 h) or placebo on day 1. Mean changes in dyspnea 45 minutes after injection were -25 +/- 10 mm and -1.2 +/- 1.2 points for morphine, versus 0.6 +/- 7.7 mm (P < 0.01) and -0.1 +/- 0.3 points (P = 0.03) for placebo. No relevant changes were observed in somnolence, pain, anxiety, respiratory effort and rate, and oxygen saturation.

[18] Allard P, Lamontagne C, Bernard P, et al. 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. PMID: 10203878. Full Text.

A randomized continuous sequential clinical trial of 33 terminally ill cancer patients with persistent dyspnea after rest and treatment with oxygen were paired. 25% of the equivalent 4-hourly dose of opioid was sufficient to reduce both dyspnea intensity and tachypnea for 4 hours.

[19] 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. PMID: 11844637.

35 patients on a dedicated oncology unit were treated with nebulized fentanyl. 81% reported improvement in breathing.

[20] Farncombe M. Dyspnea: assessment and treatment. *Support Care Cancer*. 1997;5(2):94-99. PMID: 9069607.

[21] Davis CL. The use of nebulized opioids for breathlessness. *Palliat Med*. 1995;9(2):169-170. PMID: 7606335.

[22] Mitchell-Heggs P, Murphy K, Minty K, et al. Diazepam in the treatment of dyspnea in the pink puffer syndrome. *Q J Med.* 1980;193:9-20. PMID: 6776586.

With diazepam, subjects experienced a striking reduction in dyspnea, and an improvement in effort tolerance; in addition the slope of the ventilation/CO2 response curve was reduced. There were no changes in resting blood gases.

[23] Stark RD, Gambles SA, Lewis JA. Methods to assess breathlessness in healthy subjects: a critical evaluation and application to analyse the acute effects of diazepam and promethazine on breathlessness induced by exercise or by exposure to raised levels of carbon dioxide. *Clin Sci.* 1981;61:429-439. PMID: 6793277.

6 healthy subjects. During exercise, diazepam and promethazine did not reduce breathlessness, although there was a minor trend with promethazine.

[24] Woodcock AA, Gross ER, Geddes DM. Drug treatment of breathlessness; contrasting effects of diazepam and promethazine in pink puffers. *BMJ.* 1981;283:343-346. PMID: 6788319.

Fifteen out of 18 "pink and puffing" patients completed a double-blind, placebo-controlled cross-over trial. Diazepam had no effect on breathlessness and noticeably reduced exercise tolerance. Promethazine reduced breathlessness and improved exercise tolerance without altering lung function.

[25] 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. PMID: 3780329.

Randomized, placebo-controlled double-blind study of 24 patients with alprazolam (0.5 mg bid) or placebo administered for one week, followed by placebo for one week, then either placebo or alprazolam for the third week. Alprazolam was not effective in relieving exercise dyspnea.

[26] O'Neill PA, Morton PB, Stark RD. Chlorpromazine: a specific effect on breathlessness? *Br J Clin Pharmacol.* 1985;19:793-797. PMID: 4027121.

12 healthy subjects participated in a double-blind, within-subject comparison of promethazine and placebo each given acutely by mouth. Promethazine had no significant effect on breathlessness nor on the relationship between breathlessness and ventilation. In contrast, chlorpromazine, caused a marked and statistically significant reduction in breathlessness without affecting ventilation and without causing detectable sedation.

[27] 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. PMID: 8265878.

A significant improvement in anxiety, depression and obsessive symptoms and complaints was noted in sixteen patients, age 56.9 +/- 17.0; treated for 14 days of placebo or buspirone (20 mg daily) in a double-blind, cross-over randomized trial. Arterial blood gases and respiratory mechanics did not change after treatment. There was an improvement in exercise tolerance and in the sensation of dyspnea.

[28] Bruera E, de Stoutz N, Velasco-Leiva A, et al. Effects of oxygen on dyspnea in hypoxaemic terminal-cancer patients. *Lancet.* 1993;342:13-14. PMID: 8100289.

14 patients with hypoxaemic dyspnea due to advanced cancer were randomised to receive either oxygen or air at 5 L/min by mask. Mean difference in dyspnea visual analogue scale between air and oxygen treatment was 20.5 (95% confidence interval 13.5 to 27.6). Oxygen is beneficial to patients with hypoxia and dyspnea at rest.

[29] Davis CL: Palliation of breathlessness, in von Gunten CF (ed): *Palliative Care and Rehabilitation of Cancer Patients*. Boston: Kluwer Academic Publishers; 1999:59-74. ISBN: 079238525X.

[30] Schwartzstein RM, Lahive K, Pope A, et al. Cold facial stimulation reduces breathlessness induced in normal subjects. *Am Rev Respir Dis.* 1987;136:58-61. PMID: 3605841.

Cold air directed on the face reduced breathlessness induced by an inspiratory resistive load and hypercapnia in 16 subjects (6.2 +/- 1.7 Borg scale units with no flow, 5.1 +/- 1.7 with cold air; p less than 0.002) without causing a significant reduction in ventilation.

[31] Liss HP. Grant BJB. The effect of nasal flow on breathlessness in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1988;137:1285-1288. PMID: 3144198.

8 patients air or oxygen through nasal cannula with or without topical topical lidocaine to the nasal passages. There was no significant effect of inspired oxygen concentration, gas flow, arterial oxygen tension, or arterial carbon dioxide tension on breathlessness. There was, however, a significant increase in breathlessness after nasal anesthesia from 44 +/- 3 SEM to 52 +/- 4 SEM (p less than 0.005).

[32] Burgess KR, Whitelaw WA. Effects of nasal cold receptors on pattern of breathing. *J Appl Physiol.* 1988;64:371-376. PMID: 3128527.

Cold air breathed through the nose inhibits ventilation in normal subjects; this is not related to an increase in flow resistance.

[33] Bredin M, Corner J, Krishnasamy M, et al. Multicentre randomised controlled trial of nursing intervention for breathlessness in patients with lung cancer. *BMJ.* 1999;318:901-904. PMID: 10102851. Full Text.

119 patients with small cell or non-small cell lung cancer or with mesothelioma and breathlessness experienced improvements in breathlessness, performance status, and physical and emotional states relative to control patients.

[34] Rossi G, Florini F, Romagnoli M, Bellantone T, Lucic S, Lugli D, Clini E. Length and clinical effectiveness of pulmonary rehabilitation in outpatients with chronic airway obstruction. *Chest*. 2005;127(1):105-109. PMID: 15653969.

A 20-session course of pulmonary rehabilitation provides more benefit than a 10-session course for patients with mild-to-moderate COPD.

[35] Wein S. Sedation in the imminently dying patient. *Oncology.* 2000;14:585-592. PMID: 10826317.

Sedation is a clinically important therapeutic intervention in the imminently dying patient for intractable symptoms like pain, agitated delirium, dyspnea, and existential or psychological distress.