

EPECTM-O

Education In Palliative And End-Of-Life Care For Oncology

Self-Study Module 3j:

Dyspnea

Module 3j: Dyspnea

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Abstract

Many symptoms and syndromes are commonly encountered in patients with cancer. This module first presents general approaches to symptom management, followed by management of the specific symptoms and syndromes, including: anorexia/cachexia, anxiety, constipation, depression, diarrhea, fatigue, insomnia, menopausal symptoms and sexual health, mucositis, nausea and vomiting, and skin problems.

Any symptom can be debilitating and prevent the patient and family from achieving goals that are important to them. As with other aspects of medicine, tailored management is based on the underlying etiology and pathophysiology. When several symptoms occur together, they can be interrelated and management can be complex.

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
- 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 and 90%, depending on the type and stage of cancer. (Ref. 1) (Ref. 2) (Ref. 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 patients 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.

Case

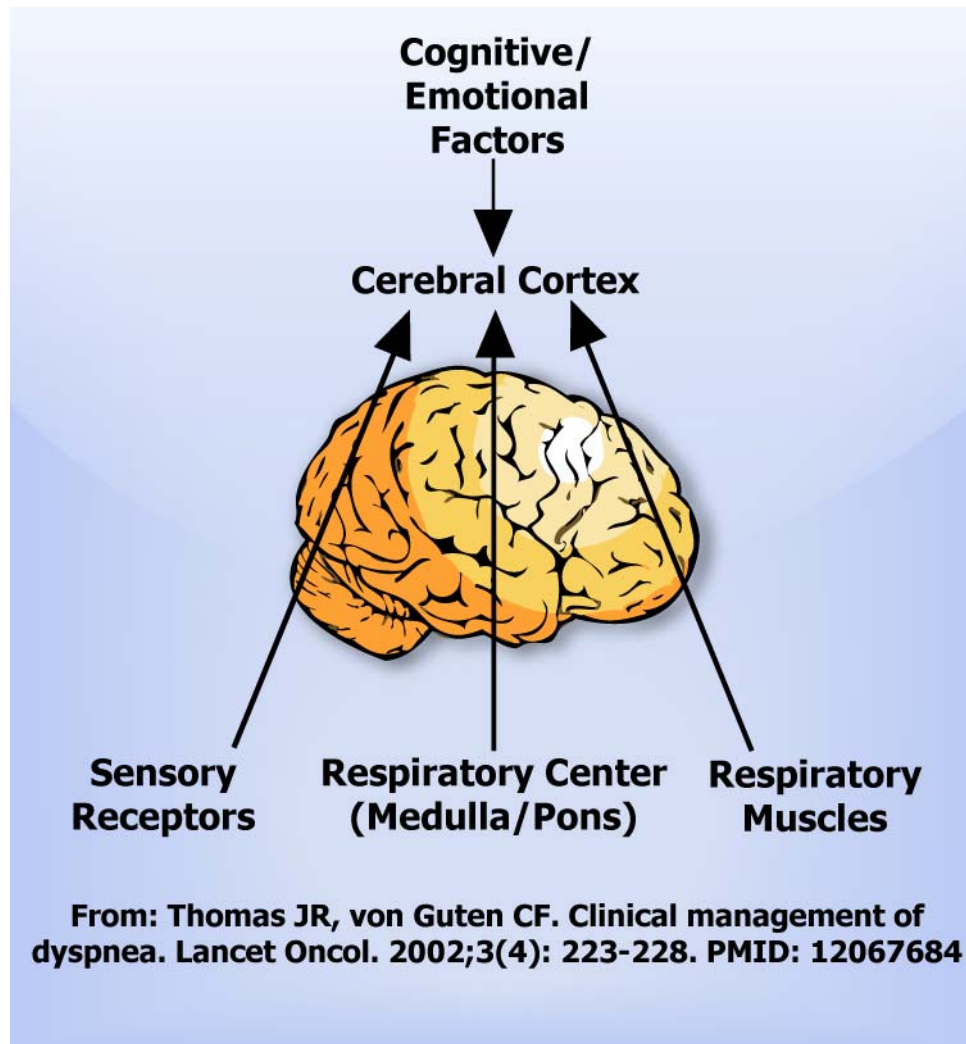
Review the case below, and keep it in mind as you progress through the module. How would you approach the assessment of this patient? What interventions might be appropriate?

M.B. is a 55-year-old longshoreman with a long history of smoking who has inoperable stage IIIb nonsmall-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.

Pathophysiology

The pathophysiology of dyspnea is multifactorial and incompletely understood (see Figure 1). (Ref. 4) (Ref. 5) (Ref. 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, and peripheral mechanoreceptors; from muscles, tendons, and joints; and from 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 that the cerebral cortex integrates this sensory input with other cognitive and emotional factors as well as with motor information from the respiratory center. (Ref. 7) (Ref. 8)

Figure 1: Schematic Representation of the Control of Respiration



Three concepts have emerged to explain the pathophysiology of dyspnea and guide therapy:

- The work of breathing
- Chemical effects
- 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, bronchial obstruction, or breathing with weakened muscles in cachexia, is sensed as dyspnea. (Ref. 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 oxygen levels. (Ref. 9) (Ref. 10) It takes moderately severe levels of hypoxemia to trigger the peripheral chemoreceptors. (Ref. 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.

Neuromechanical dissociation

Dyspnea occurs when there is a mismatch between what the brain desires for respiration and the sensory feedback it receives. (Ref. 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. (Ref. 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. Pain measurement scales can be found in EPEC™-O Module 2: Cancer Pain Management.

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 or crackles
- Inability to clear secretions
- Stridor
- Bronchospasm (wheezing)
- Central or peripheral cyanosis
- Intercostal retractions
- Tachypnea

Simple studies such as pulse oximetry, complete blood count, and 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 (e.g., bronchodilators or stent placement to relieve focal obstruction) are appropriate in selected patients (see the Appendices for strategies to manage selected causes).

To manage the experience of shortness of breath, both pharmacologic and nonpharmacologic 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 helpful. 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. (Ref. 14) (Ref. 15) (Ref. 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. (Ref. 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. (Ref. 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 both:

- An extended-release formulation for baseline dyspnea control.
- An immediate-release formulation of the same opioid for breakthrough dyspnea (e.g., 10% of the total dose q 24 h, offered q 1 h PRN).

Nebulized opioids

Nebulized opioids have been reported to offer additional relief in uncontrolled studies. (Ref. 19) However, their use remains controversial. In small randomized, controlled trials, nebulized water gave the same relief as nebulized morphine or hydromorphone. (Ref. 20) (Ref. 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 (e.g., benzodiazepines) are frequently prescribed for anxiety related to dyspnea. However, when tested, the evidence for their effectiveness is not persuasive. (Ref. 22) (Ref. 23) (Ref. 24) (Ref. 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 relatively 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. (Ref. 26) (Ref. 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, the perceived benefit of oxygen among dyspneic cancer patients far exceeds the number who have hypoxemia. (Ref. 28) (Ref. 29) It is likely that there is a placebo effect of oxygen itself 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 (e.g., from a breeze or fan). This may be explained by stimulation of the trigeminal nerve (V2 branch), which has central inhibitory effects on dyspnea. (Ref. 30) (Ref. 31) (Ref. 32) Thus, the effect of oxygen may be due in part to this sensory stimulation rather than correction of hypoxemia or a pure placebo effect.

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

Cognitive/behavioral interventions

Dyspnea also has both cognitive and emotional components. (Ref. 33) This has been well understood by pulmonary rehabilitation clinics for COPD. (Ref. 34) Instructing patients in breathing control, activity pacing, relaxation techniques, and psychosocial support is an effective method of controlling dyspnea.

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 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. (Ref. 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 life, there can be significant changes in a patient's breathing patterns (e.g., Cheyne-Stokes breathing or short, shallow respirations). These 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 retractions on examination (i.e., 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 (e.g., albuterol) to cause adverse cardiac effects in patients with cardiac compromise must be carefully considered. Frail patients may have difficulty 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 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, consider the following therapies to dry secretions:

- **Scopolamine**, 0.1-0.4 mg SC, IV q 4 h or 1-3 transdermal patches q 72 h or 10-80 µmg/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 than 10 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 symptomatic benefit, do not follow the hematocrit or repeat transfusions.

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) or 40,000 IU SC weekly.
- Double the dose if the hemoglobin does not increase by more than 1 g/dl within 4 weeks. **Darbepoietin** weekly or every other week 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)
- Management of 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 dyspnea to the satisfaction of the majority of patients. Oxygen and benzodiazepines may be useful adjuncts. While many clinicians fear that respiratory depression may occur with the use of opioids and benzodiazepines for dyspnea control, this fear is unwarranted as long as accepted dosing guidelines are followed. 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 respiratory rate, hemoglobin oxygen saturation, or blood gas concentrations as long as dosing guidelines are followed.
2. Opioid treatment for dyspnea is consistent with good medical practice and is 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 by breathless patients to be helpful, it is just as likely due to the placebo effect, a local breeze, and cooling of the skin around the nares as to the reversal of hypoxemia.

Pearls

1. Titrate opioids to the patient's report of relief; misadventures occur when titrating to the relief of onlookers such as family or health care professionals.
2. In the United States, hospice programs can provide oxygen without demonstration of hypoxemia.
3. Make a partnership with your patient and the family caregiver; draw them into the interdisciplinary team and foster their active participation in the care plan.
4. Additional information can be found in Module 3: Patient Resources.

Pitfall

1. Titrating to respiratory rate-it is not a measure of breathlessness

Appendix 1: Cough Medication Table

Cough Medication Table

Cough (antitussives)								
Generic Name	Trade Name(s)	Dosage Forms/ Time C _{max}	Elimination t _{1/2}	Route of Elimination	Adult Doses	Pediatric Doses	Adverse Effects	Common Interactions
Dextromethorphan Antitussive	Various combination preparations: cap: 30 mg syrup: 30 mg/5 ml	PO: 2-2.5 hr	1.4-3.9 hr Metabolites: 3.4-5.6 hr	Liver metabolism: rate of metabolism varies among individuals Renal excretion: extensive	15-45 mg PO q 4-6 h PRN max 120 mg/24h	1 mg/kg/24h ÷ q 6-8 h	<ul style="list-style-type: none"> • nausea/vomiting • dizziness • sedation • GI disturbances 	<ul style="list-style-type: none"> • CNS depressants • MAOIs
Hydrocodone Antitussive opioid	Various; Hycodan® is an example: tab: 5 mg syrup: 5 mg/5 ml	PO IR: 1.3 hr PO ER: 3.4 hr	3.8-4.5 hr	Liver metabolism: extensive Renal excretion: 26%	5-10 mg PO q 4-6 h PRN	0.1 mg/kg PO q 4 h PRN	<ul style="list-style-type: none"> • lightheadedness • dizziness • sedation • nausea/vomiting • constipation • hypersensitivity 	<ul style="list-style-type: none"> • CNS depressants • TCAs • MAOIs

Appendix 2: Drying Medication Table

Drying Medication Table

Drying (anti cholinergics)								
Generic Name	Trade Name(s) Dosage forms	Time Cmax	Elimination t _{1/2}	Route of elimination	Adult doses	Pediatric doses	Adverse effects	Common interactions
Atropine Antimuscarinic anticholinergic	Various: inj: 0.1, 0.4, 0.5 1.0 mg/ml in multiple combination PO tablets	PO: 1 hour IM: 30 minutes	Biphasic: initial ~ 2 hours; final: 12.5-38 hours	Liver metabolism: 45% Renal excretion: 30-50% unchanged	0.4-0.6 mg SC, IM, IV q 3-4 h routinely or prn	0.01-0.02 mg/kg SC, IM, IV	<ul style="list-style-type: none"> • CNS and cardiac excitation (atropine only) • anticholinergic AE • photophobia • palpitations, tachycardia (atropine only) • constipation • difficulty urinating 	<ul style="list-style-type: none"> • antacids, histamine H₂ receptor antagonists may interfere with absorption • amantadine, quinidine • haloperidol • phenothiazines • MAOIs • TCAs
Glycopyrrolate Anticholinergic	Robinul®: tab: 1, 2 mg inj: 0.2 mg/ml	PO: 90 minutes IM: 10 minutes	2.2-33.4 minutes	Renal excretion: 48.5%	0.1-0.4 mg IM, IV q 4- 6 h PRN	☺	<ul style="list-style-type: none"> • anticholinergic AE 	<ul style="list-style-type: none"> • antacids • slow K • levodopa • digoxin • phenothiazines • amantadine • antiparkinsonian agents • glutethimide
Hyoscyamine Antimuscarinic anticholinergic	Various; Levsin®, Cystospaz® are examples: tab: 0.125 mg drops: 0.125 mg ER: 0.375 mg	PO SR: 2.5 hr	3.5 hr ER: ≈ 7 hr	Renal excretion: majority of hyoscyamine excreted unchanged in urine within 12 hr	0.125-0.25 mg PO SL q 4 h routinely or PRN (max 1.5 mg/24h)	2-10 y: 0.25- 1.0 ml PO q 4 h routinely or PRN	<ul style="list-style-type: none"> • drowsiness (scopolamine) • nausea/vomiting • delirium, coma 	<ul style="list-style-type: none"> • some antihistamines • digoxin • ketoconazole

Drying (anti cholinergics)								
Generic Name	Trade Name(s) Dosage forms	Time Cmax	Elimination t1/2	Route of elimination	Adult doses	Pediatric doses	Adverse effects	Common interactions
Scopolamine Antimuscarinic anticholinergic	Various; Transderm- Scop® is an example: inj: 0.4 mg/ml patch: contains 1.5 mg, releases 1.0 mg in 3 days	4 hr	9.5 hr	Liver metabolism: extensive Renal excretion: 1% (oral), 34% (transdermal)	0.3-0.6 mg SC, IV, IM q 4 h–8 h PRN or by continuous SC, IV infusion, or 1-2 patch(es) behind alternating ears q 72h (patch takes 12 h to achieve maximum blood levels, and 12 h after removal of last patch to clear scopolamine from the blood) (wash hands thoroughly after applying patch)	not indicated for children	<ul style="list-style-type: none"> may precipitate acute confusion or dementia-like picture, acute glaucoma; discontinue immediately contraindicated in presence of dementia, delirium, or glaucoma treat excess with physostigmine IV hypersensitivity 	<ul style="list-style-type: none"> antacids; histamine H₂ receptor antagonists may interfere with absorption amantadine, quinidine haloperidol phenothiazines MAOIs TCA's

Appendix 3: Dyspnea Medication Table

Dyspnea Medication Table

Dyspnea (bronchodilators)								
Generic Name	Trade Name(s) Dosage forms	Time Cmax	Elimination t1/2	Route of elimination	Adult doses	Pediatric doses	Adverse effects	Common interactions
Albuterol Inhaled β_2 adrenergic agonist	Various; Ventolin [®] is an example: MDI: 6.8, 17-g canister = 100 μ g/puff 0.5%, 0.83% inhalation solution syrup: 2 mg/5 ml tab: 2, 4 mg	Aerosol inhalation: 3-4 hr SL: 2-3 hr ER: 6 hr PO: 1-4 hr	3-6.5 hr	Liver metabolism: to active metabolites 64%-98% Feces: 1.2-7% after PO dose 10.2-12% after inhalation	2.5-5.0 mg solution diluted– 4.0 ml with NS nebulized q 4 h PRN, or 2-3 puffs metered-dose inhaler q 4 h PRN 2-4 mg PO tid-qid	0.03 ml/kg in 3 ml normal saline via nebulizer PRN child over 12: 2 mg PO qid	<ul style="list-style-type: none"> tremor nervousness tachycardia 	<ul style="list-style-type: none"> CNS stimulants levodopa propranolol MAOIs TCAs
Theophylline Bronchodilator	Various; Theo-Dur [®] is an example: tabs: 100, 125, 200, 300, 450, 600 mg	PO once-a-day dosage form: 11 hr	6-12 hr, adults	Liver metabolism: extensive Renal excretion: 10%-13%, adults	start with 200-300 mg PO q 12 h every 3 days; increase 50-100 mg q 12 h until response or toxicity (monitor blood levels)	6 wk-1 y: 6-15 mg/kg/24h \div q 6-8 h 1-12 y: 20 mg/kg/24h \div q 8-12 h 12-16 y: 18 mg/kg/24h \div q 12 h	<ul style="list-style-type: none"> nervousness restlessness dizziness insomnia palpitations nausea/vomiting 	<ul style="list-style-type: none"> adenosine barbiturates carbamazepine phenytoin rifampin cimetidine

Appendix 4: Steroids Medication Table

Steroids Medication Table

Steroids (glucocorticoids and mineralocorticoids)								
Generic Name	Trade Name(s)	Dosage Forms/ Time C _{max}	Elimination t _{1/2}	Route of Elimination	Adult Doses	Pediatric Doses	Adverse Effects	Common Interactions
Dexamethasone Glucocorticoid	Various; Decadron® is an example: tabs: 0.5, 0.75, 2, 4, 6 mg elixir: 0.5 mg/ml inj: 4, 10 mg/ml	PO cap: 3.17 hr PO elixir: 10-60 minutes PO tabs: 1-2 hr	Plasma: 1.88-2.23 hr Biological duration of action: 36-54 hr	Liver metabolism: partial Renal excretion: up to 65% Bile: small extent	0.5-8 mg PO, IV, IM, SC daily-q 6 h (single doses of 40-100 mg IV may be used to effect an acute response) (dosage may need to be tapered slowly to avoid adrenocorticoid insufficiency on withdrawal)	††	<ul style="list-style-type: none"> increased risk of infection, particularly opportunistic infections gastritis, gastric ulceration/bleeding, nausea/vomiting pancreatitis wasting, particularly proximal muscles thinning of skin, bowel (possible perforation), impaired wound healing salt, water retention, hypertension, cushingoid state 	<ul style="list-style-type: none"> hepatic microsomal enzyme inducers estrogens NSAIDs K⁺ depleting drugs anticholinesterase agents PO anticoagulants cyclosporine
Fludrocortisone acetate Mineralocorticoid	Florinef®: tab: 0.1 mg	PO: 1.7 hr	3.5 hr	Liver metabolism: extensive	0.1-0.2 mg PO daily (may combine with glucocorticoid)	50-200 µg PO daily	<ul style="list-style-type: none"> increased risk of infection, especially fungal, TB, other opportunistic infections salt, water retention, hypertension hypokalemia 	<ul style="list-style-type: none"> K⁺ depleting drugs

Steroids (glucocorticoids and mineralocorticoids)								
Generic Name	Trade Name(s)	Dosage Forms/ Time C _{max}	Elimination t _{1/2}	Route of Elimination	Adult Doses	Pediatric Doses	Adverse Effects	Common Interactions
Prednisone Glucocorticoid	Various: tabs: 1, 2.5, 5, 20, 50 mg Soln: 1, 5mg/ml	PO: 1.3 hr	Plasma: 2.6-3 hr Biological duration of action: 12-36 hr	Liver metabolism: extensive (metabolized to the biologically active steroid, prednisolone)	5-80 mg PO daily	††	<ul style="list-style-type: none"> • hyperglycemia • euphoria, insomnia, mood swings, personality changes, depression, psychosis • withdrawal may lead to adrenocortical insufficiency, flair in joint pain • may suppress reactions to skin tests • not to be used in presence of herpes zoster 	<ul style="list-style-type: none"> • hepatic microsomal enzyme inducers • estrogens • NSAIDs • K⁺ depleting drugs • anticholinesterase agents • PO anticoagulants • cyclosporine

References

Module 3j: Dyspnea

- 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.

Two hundred eighty-nine unselected patients were included in this study; 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 with the 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. Eighteen (21%) patients developed dyspnea as their main symptom, and this was 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%, with prevalence rates generally exceeding 50% at any of three measurements. Underlying lung and/or cardiac disease 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% of dyspneic patients. In 23.9%, neither lung nor 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 $p\text{CO}_2$ 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 that severe respiratory muscle weakness may have contributed 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 eight 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.

In this study, 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 pCO₂ 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 (e.g., "short of breath" or "air-starved") when end-tidal pCO₂ increased 10 Torr (mean) above 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 airway 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 nine 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 proven beyond doubt to explain mechanisms responsible for the onset of sensory discharges in the carotid nerve. The multitude of biochemical and biophysical processes (some of them still unknown) operating at different receptor levels has made it 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.

Twenty-three patients with chronic airflow limitation had significantly ($p < 0.01$) higher levels of ventilation (% maximal voluntary ventilation) for a given work rate (slope of $VE[\%MVV]/WR[\% \text{ pred max}] = 1.51 \pm 0.18$ versus 0.63 ± 0.10 ; mean \pm SEM) and greater dynamic lung hyperinflation (DH) (change [Δ] in end-expiratory lung volume [EELV_{dyn}] = $+0.31 \pm 0.11$ 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 (EELV_{dyn} = 75 ± 3 versus $46 \pm 6\%$ 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 at 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% and increased exercise tolerance by 18%. 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 with COPD substantially increased their exercise capacity. The improved exercise tolerance appeared 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.

Ten 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 crossover 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 7 opioid-naïve patients and 3.75 mg in 2 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.

Thirty-five 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.

In a survey of six healthy subjects during exercise, diazepam and promethazine did not significantly reduce breathlessness, although there was a minor trend toward improvement 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 crossover 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.

A randomized, placebo-controlled double-blind study of 24 patients with alprazolam (0.5 mg bid) or placebo administered for 1 week, followed by placebo for 1 week, then either placebo or alprazolam for the third week was conducted. 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.

Twelve 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 or 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 16 patients, age 56.9 +/- 17.0; treated for 14 days of placebo or buspirone (20 mg daily) in a double-blind, crossover randomized trial. Arterial blood gases and respiratory mechanics did not change after treatment. There was an improvement in exercise tolerance and 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.

Fourteen patients with hypoxaemic dyspnea due to advanced cancer were randomized 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; $p < 0.002$) 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.

Eight patients received air or oxygen through nasal cannula with or without 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 ($p < 0.005$).

- 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.

In this study 119 patients with small-cell or nonsmall-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, et al. 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 provided 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 such as pain, agitated delirium, dyspnea, and existential or psychological distress.

Self-Assessment

Module 3j: Dyspnea

8. When a patient is treated with morphine for breathlessness, the drug is titrated to:
- ☐ a). respiratory rate
 - ☐ b). pulse oximetry
 - ☐ c). patient's relief
 - ☐ d). oxygen concentration
-

Self-Assessment Answers

Question 7. The correct answer is: c)

This question is aimed at understanding how to symptomatically treat breathlessness. Patient self-report is the gold standard. Neither respiratory rate, pulse oximetry, nor blood oxygen concentration will tell you whether breathlessness is relieved.