

Symptoms and Syndromes



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Disclosure Statements

- None of the presenters have any conflicts to disclose

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Objectives

- **Learn general guidelines for managing non-pain symptoms**
- **Understand how the principles of intended/unintended consequences and double effect apply to symptom management**
- **Know the assessment, management of common physical symptoms**

General Management Guidelines...

- **History and Physical examination**
- **Conceptualize likely causes**
- **Discuss treatment options, assist with decision making**

...General Management Guidelines

- **Provide ongoing patient, family education, support**
- **Involve members of the entire interdisciplinary team**
- **Reassess frequently**



Rationalize Management

- **Multiple Symptoms**
- **Optimize non-invasive, non-pharmacological approaches**
- **Avoid polypharmacy if possible**
 - Use 1 agent for 2 symptoms if possible
 - Consider adverse effects and interactions
 - Use renal and hepatic dosing as needed

Intended vs. Unintended Consequences

Primary intent dictates ethical medical practice

Four Elements of The Principle of Double Effect

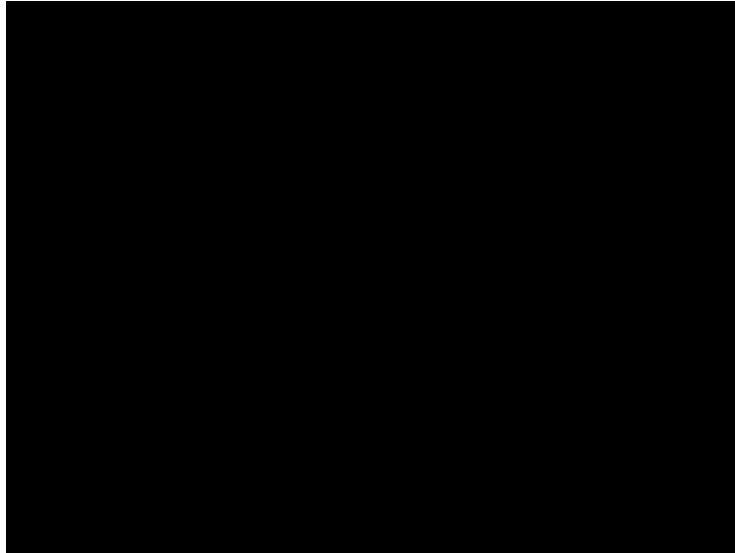


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Dyspnea

Jeanine Famiglietti, MD



Breathlessness (dyspnea) . . .

May be described as:

- Shortness of breath
- a smothering feeling
- inability to get enough air
- suffocation



... Breathlessness (dyspnea)

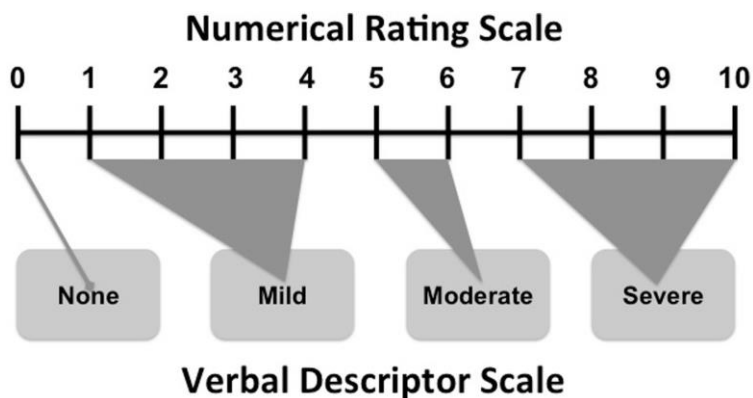
- The only reliable measure is patient self-report
- Respiratory rate, pO_2 , blood gas determinations **DO NOT** correlate with the feeling of breathlessness
- Prevalence in the life-threateningly ill: 12 – 74%

Measuring Breathlessness

- Patients should use a simple tool
- A numerical 11 point rating scale between 0 to 10 is reliable and valid for measuring change in breathlessness in individual patients.
- In patients unable to report can use the validated respiratory distress observation scale

Ekstrom MP, et al. The Management of chronic breathlessness in patients with advanced and terminal illness. BMJ 2015 . 349: 7617.

Dyspnea Scale



Three Categories

- **Work of breathing caused by increased airway resistance or weakened muscles**
- **Chemical causes, including hypercapnia and hypoxia**
- **Neuromechanical dissociation, a mismatch between what the brain expects as respiration and the signals it receives**

Causes of Chronic Breathlessness in 129 Patients in Primary Care

- **Respiratory 53%**
- **Asthma, COPD, ILD, PAH, other**
- **Cardiac 21%**
- **Heart failure, Ischemia heart disease, Valvular heart disease, anemia, other**
- **Obesity 16%**
- **Deconditioning 4%**

Ekstrom et. al. BMJ 2015;349:g7617

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Causes of Breathlessness

Anxiety

Airway Obstruction

Bronchospasm

Hypoxemia

Pleural Effusion

Pneumonia

Pulmonary Edema

Pulmonary Embolism

Thick Secretions

Anemia

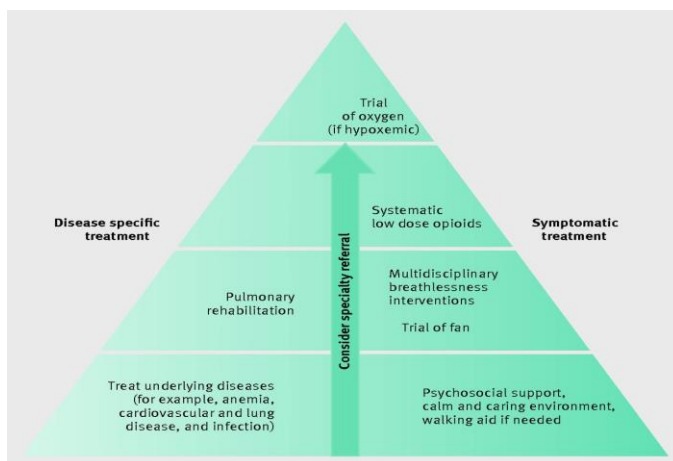
Metabolic

**Family/Financial/Legal
/Spiritual/Practical
Issues**

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Kamal et al. Journal of Palliative Medicine Vol. 15, Number 1, 2012

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Management of Breathlessness

- **Treat the Underlying Cause**
- **Symptomatic Management**
 - **Non Pharmacologic Interventions**
 - **Pharmacologic Interventions**

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Specific Causes and Treatments

- **Bronchospasm** - nebulized albuterol and ipratropium and/or inhaled steroid, systemic steroid if lung tumor
- **Rales** - Reduce or stop IV fluids and artificial feedings, diuretics, antibiotics for pneumonia based on goals of care
- **Effusions** - Thoracentesis may be effective, pleurodesis or chest tube drainage
- **Airway obstruction, aspiration** - clean trach appliances, modify diet, positioning, suction when appropriate

Tucker et al. Managing non pain symptoms

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Specific Causes and Treatments

- **Thick Secretions** - loosen secretions with Guaifenesin or nebs, treat thin secretions with atropine, scopolamine, or glycopyrrolate
- **Hemoglobin low** - transfusion depending on goals of care
- **Anxiety** - treat anxiety with relaxation techniques, benzo's or antidepressants
- **Interpersonal issues** - Counseling
- **Religious concerns** - Spiritual Care

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More General Interventions

- **Oxygen**
- **Pulmonary Rehabilitation**
- **Relaxation techniques and psychosocial support, guided imagery**
- **Modification of activity and walking aids**
- **Use of a fan to blow air over the face, humidified air, wipe face with damp cloth**
- **Changing positions and pursed lip breathing**

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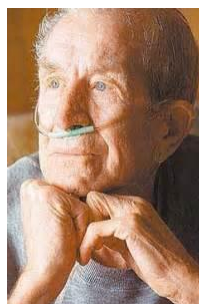
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Oxygen

- **Pulse oximetry not helpful**
- **Potent symbol of medical care**
- **Expensive**
- **Fan may do just as well**



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Oxygen

- **Studies of supplemental oxygen for relief of dyspnea have shown mixed results**
- **Supplemental oxygen is standard therapy for symptomatic management of patients who are hypoxemia on room air.**
- **Perceived benefit of oxygen therapy extends beyond its ability to reverse hypoxemia**

Mechanisms by Which Supplemental Oxygen May Reduce Dyspnea

- **Reversal of hypoxemia**
- **Reduced serum lactic acid**
- **Reduced pulmonary artery pressure**
- **Reduced dynamic hyperinflation**
- **Reduced ventilatory muscle and diaphragm fatigue**
- **Relief of broncho constriction**
- **Stimulation to facial, nasal , or pharyngeal receptors**
- **Increased capacity for exercise training**
- **Placebo effect**

Oxygen use in non-Hypoxemic Patients

- **The Oxygen Trial randomized 239 patients with refractory dyspnea and adequate PaO₂ to oxygen or room air administered via N/C**
- **There is no difference between oxygen and room air via nasal cannula for the treatment of refractory dyspnea in non-hypoxemic patients.**
- **Best first intervention may be a handheld fan or rotating fan in the room, along with opioids**

LeBlanc, Thomas and Abernethy, Amy. Building the Palliative Care Evidence Base: Lessons from a Randomized Controlled Trial of Oxygen vs. Room Air for Refractory Dyspnea. J Natl Compr Canc Netw. 2014 July; 12(7): 989-992

Studies of Fan Use

- **Feasibility study May 2016 in Journal of Pain and Symptom Management showed overall benefit of handheld fan use in patients with refractory breathlessness**
- **Study in American Journal of Hospice and Palliative Medicine Oct 2015 showed Chinese patients with terminal cancer showed a significant difference NRS scores of experimental groups indicating significant reduction in sensation of breathlessness**



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Non-Invasive Ventilation

- In a recent study of 200 patients with advanced cancer and severe respiratory failure, NPPV was shown to improve dyspnea much faster than passive oxygen therapy.
- The dose of morphine needed to control dyspnea was significantly less.

Nava, S. et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumors: a randomized feasibility trial. *Lancet Oncol* 2013;14:219-27.

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Non-Invasive Ventilation

- **Improves breathlessness in hypercapneic respiratory failure in COPD**
- **Should only be used if tolerated by the patient and provides symptom relief. Goals of the intervention should be established in advance**

Nava, S. et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumors: a randomized feasibility trial. *Lancet Oncol* 2013;14:219-27.

High-Flow Nasal Cannula

- **New Technology in treating hypoxemic respiratory failure**
- **Can deliver up to 60 L/min, FIO₂ ranging from .21 – 1**
- **Leads to reduction in respiratory rate, hypoxemia, and reduction in dyspnea compared with nasal cannula**
- **Can allow patients to talk and eat, more expensive but more comfortable**
- **Must be carefully considered in context of patient's goals, can lead to ethical and communication dilemmas**

Shah, Nidhi et al. Fast Facts and Concepts # 330 High-Flow Nasal Canula Oxygen Therapy in Palliative Care



Opioids

- **First-line pharmacologic agents for managing nonspecific dyspnea in patients with advanced disease.**
- **Multiple expert groups recommend the use of systemic opioids for relief of dyspnea in patients with advanced disease.**
- **Morphine is most studied however no studies demonstrate one opioid as having clear benefits over the others.**

Theory of Mechanisms of Opioids

- **Dampen the chemoreceptors ability in the brainstem to detect hypercapnia and hypoxia**
- **With a decreased respiratory output, assumption made of decrease in corollary discharge to the sensory cortex**
- **Can effect central processing of dyspnea. Neuroimaging studies evidenced how air hunger associated with higher brain centers**
- **It is believed that opioid receptors are located in alveolar walls, trachea, and main bronchi**

Gelot, Shyam et al. Review of Opioid Use in Palliative Care Patients with Refractory Dyspnea. Austin J Pharmacol Ther. 2013;1(1):1002

More Mechanisms

- **Increase peripheral vasodilatation with a decrease in cardiac preload.**
- **Decrease anxiety and the subjective feeling of dyspnea.**
- **May alter perception of dyspnea at different levels of the afferent pathways**

Tucker, Rodney O., et al. Managing Nonpain Symptoms

Role of Endogenous Opioids

- Exogenous opioids work by mimicking the body's endogenous opioids
- Recent evidence has shed light on the role of endogenous opioids as a natural mechanism in relieving dyspnea
- A trial conducted in 17 COPD patients undergoing exercise testing showed a 3 fold increase in B-endorphins after 10 minutes. Symptoms were higher in the group given naloxone, suggesting role of endogenous opioids in decreasing dyspnea.

Gelot, Shyam et. al. Review of Opioid Use in Palliative Care Patients with Refractory Dyspnea. *Austin J Pharmacy Ther.* 2013;1(1): 1002

Studies Supporting Use of Opioids

- First reported by Light and colleagues in 1989
- First adequately powered study was in 2003, conducted by Abernethy and colleagues. Study involved 48 opioid naïve patients, who were randomized to 4 days of 20 mg SR morphine f/b 4 days placebo. Patients reported better dyspnea scores, better sleep, but not powered to detect differences of side effects.

Which Opioid dose is needed?

- **Study by Currow aimed to determine minimum effective once daily dose of SR morphine and whether net clinical benefits are sustained safely**
- **10 mg daily of SR morphine was administered and increased in non responders by 10 mg daily each week to max of 30 mg daily. Response rate was 62%. For 70% dose was 10 mg /24hrs. Benefit was maintained at 3 months for 33 % of people. Breathlessness reduced significantly.**
- **No respiratory depression, constipation increased.**

Currow DC, et al. J Pain symptom Manage 2011;42-388-99.

Recommendations From Expert Groups

- **The American Thoracic Society, ACCP, and the Canadian Thoracic Society recommend the use of oral and parenteral opioids in the treatment of dyspnea.**
- **Based on establish trials for demonstrating efficacy, dose initiation, and lack of major adverse effects.**
- **Nebulized opioids not recommended due to lack of evidence. However, a trial of nebulized treatment can be considered for patients who have adverse effects on small doses of opioids**

Currow, DC et al. J Pain Symptom Management 2011;42:388-99

Guidelines for Starting Doses of Opioids

- **Mild to moderate dyspnea in opioid naive patients:** hydrocodone 2.5 to 5 mg every 4 hours, morphine 2.5 to 5 mg po every 4 hours
- **Severe dyspnea in opioid naive patients:** Morphine 5 mg every 4 hours, oxycodone 5 mg every 4 hours, hydromorphone 1 to 2 mg every 3 or 4 hours
- **If dosage not sufficient, may be titrated upward by 25% to 50% every 12 to 24 hours**
- **For opioid tolerant patients use the opioid the patient is already taking and titrate to efficacy**

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Chronic Dyspnea

- **Most commonly patients with severe COPD, may fare worse with episodic as needed doses**
- **May need scheduled doses of opioids**
- **A dose-finding study suggests regular sustained release opioid initiated in a dose equivalent to 10 mg oral morphine daily**
- **Titrated upward, preferable once weekly, balancing both beneficial and adverse effects**
- **All patients should receive prophylaxis and treatment against constipation**

Opioid Safety

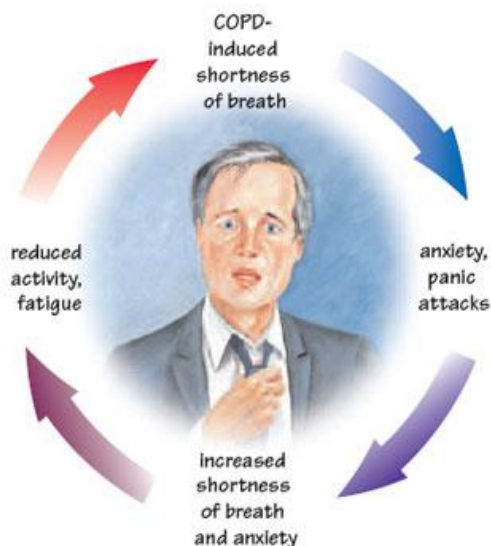
- **Usual barrier to use for treatment of dyspnea is fear of respiratory depression and accelerated death**
- **Incidence is low if opioid dosing is managed appropriately**
- **With proper titration opioids can be used to relieve dyspnea by decreasing respiratory rate while avoiding iatrogenic hypercarbia or hypoxia**

Kamal et al. Journal of Palliative Medicine Vol 15, 1 2012

Opioid Safety

- **Benzodiazepines and higher dose opioids were associated with increased adjusted mortality**
- **Lower dose opioids were not associated with increased risk of admission or death in patients with COPD**
- **Sustained release morphine should be considered first line, initiated at low dose and titrated over days or weeks**

Ekstrom et al. BMJ 2014;348:g445



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Benzodiazepines

- Patients often experience vicious cycle in which dyspnea induces anxiety and anxiety amplifies dyspnea
- A Cochrane Database review revealed no evidence for a beneficial effect of benzodiazepines for relief of breathlessness for advanced cancer and COPD. There was a slight trend towards effect but size small.
- Benzos caused more drowsiness compared to placebo

Cochrane Database Syst Rev 2010 Jan 20 (1)

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More About Benzodiazepines

- **Consider second or third line when opioids or non-pharmacological measures have failed to control breathlessness.**
- **Should be reserved for refractory dyspnea compounded by anxiety symptoms**
- **Benzodiazepines and opioids can be safely combined in low doses**
- **Adequate follow up of patients clinical condition and symptoms necessary**

More About Benzodiazepines

- **In a population based cohort study, benzodiazepines and opioids were not associated with increased admission**
- **Benzodiazepines were associated with increased mortality with a dose response trend**
- **Opioids at lower dose, 30 mg or less oral morphine equivalents a day were not associated with increased mortality in contrast with higher opioids**
- **Concurrent benzodiazepines and opioids in lower doses were not associated with increased admissions or mortality**

Ekstrom, Magnus et al. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. BMJ 2014;348:g445

More About Benzodiazepines

- Clonazepam .25 mg po every 12 hours can be useful in chronic dyspnea
- Alprazolam may be too short acting
- Lorazepam provides more rapid onset than clonazepam but lasts 4 to 6 hours. (Available in oral concentrate that can be given sublingually when oral intake is difficult.)

Other Medications

- Antidepressants - current evidence is inconsistent
- Inhaled saline - a randomized trial of 40 people showed no consistent relief
- Inhaled furosemide - results for efficacy conflicting, needs to be confirmed in large clinical trials
- Steroids - for svc syndrome or diffuse parenchymal metastasis



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Congestion and Terminal Secretions

- **Education - support family at bedside, drowning and suffocation are not accurate descriptions of what is going on**
- **Avoid term “Death rattle”, instead use congestion**
- **Prepare the family for what to expect**

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Cochrane Review

- In an updated Cochrane Review in 2008, It was concluded that there was no evidence to show that any intervention , be it pharmacological or non-pharmacological was superior to placebo in the treatment of noisy breathing.
- Clinicians need to reassure family members and staff about the unlikelihood that the patient is experiencing discomfort

Non-Pharmacological Treatment

- Repositioning - move from supine to lateral recumbent with head slightly raised
- Suctioning - most secretions are below the larynx and are inaccessible, routine use needs to be discouraged
- Provide good mouth care, avoid over hydration

Anti-Cholinergics

- Most use because of their side effect profile to dry up secretions and congestion
- Atropine ophthalmic solution, 1 to 4 drops q 4 h or prn sublingual
- Scopolamine transdermal patch, 1 to 3 patches, q 72 hours (slow onset 8 to 12 hours)
- Glycopyrrolate .2 to .4 mg (po, iv, sc) q 3 hours as needed. Does not cross BBB

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Cough



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Cough Reflex Arc

- **Afferent Pathway – Sensory nerve fibers (branches of vagus nerve) in ciliated epithelium of upper airways and cardiac and esophageal branches from diaphragm**
- **Central Pathway (cough center) – located in upper brainstem and pons**
- **Efferent pathway – impulses from cough center travel via the vagus, phrenic, and spinal motor nerves to diaphragm, abdominal wall and muscles**

Polverino et al. Multidisciplinary Respiratory Medicine 2012, 7:5

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Management

- **Cough Assement – cough acronym O,P,Q,R,S,T,U,V (onset, provoking, quality, region, severity, treatment, understanding impact on you, values)**
- **Treat the underlying cause with disease directed therapy**
- **Non pharmacological treatment**
- **Pharmacological symptom directed treatment**

Irwin RS, Diagnosis and Management of Cough-Executive Summary 2006 January

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Non pharmacological Treatment

- **Positioning**
- **Avoidance of smoking and irritants**
- **Nebulized saline or humidifier**
- **Adequate hydration**
- **Suctioning in patients with tracheostomy, esophageal obstruction or bleeding**
- **Anxiety reduction strategies**
- **Linctus - honey**

Pharmacological treatment

Antitussives

- **Centrally acting**
 - Dextromethorphan**
 - Opioids**
 - Gabapentin**
- **Peripherally acting**
 - Benzonatate**
- **Other**
 - Bronchodilators**
 - Steroids**
 - Sodium Cromoglycate**

Recommendations

- In opioid naïve patients, may consider codeine 15 mg Q 4 hrs, hydrocodone 5 mg (only combination available in US) or morphine 5 mg Q 4 hrs
- For patients already receiving opioids for pain, a 25-50% increase may be tried
- Data inconsistent for dextromethorphan
- Gabapentin recommended by ACCP for unexplained chronic cough
- Benzonatate anesthetizes stretch receptors in lungs and pleura, anecdotal evidence
- Selected patients may benefit from bronchodilators, steroids, sodium cromoglycate

Conclusion

- Dyspnea is a subjective sensation that may be influenced by physical, psychological, social, and spiritual factors
- Optimal treatment of the underlying illness using a team based approach is best
- Consider using non pharmacological modalities first
- Ongoing communication with family and caregivers is key
- Consider low dose opioids