



Hospice Pharmacotherapy 101: Pain & Dyspnea

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Disclosure

- I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this presentation.
 - This discussion will include the use of medications for off-label indications.
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Objectives

- Identify underlying causes of pain and dyspnea
 - Discuss various assessment tools and strategies for management of pain and dyspnea
 - Review available pharmacologic treatment options to help guide appropriate medication selection and dosing
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Pain Management

Types of Pain
Pain Assessment
Treatment

Patient Case: Mrs. Amanda Anderson

45 year old female admitted to hospice with recurrent breast cancer and lung metastases. She has a tumor in her breast that can be palpated inside her right axilla. Two days ago she began to notice increasing pain in her right armpit and new pain in her left hip, worse with movement and interfering with ability to sleep. Patient is primary caregiver for 2 children under the age of 10, and has a supportive husband who works full time outside of their home.

PMH: diabetes, tobacco use

Allergies: codeine

Medications:

-Glucophage (Metformin®) 1000mg by mouth twice daily

-Glucotrol (Glipizide XL®) 10mg by mouth every morning

-Ibuprofen 200-400mg by mouth every 6-8 hours as needed for pain

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Patient Case: Mrs. Amanda Anderson

Pain regimen: She has been taking Ibuprofen with minimal relief.

Pain is described as constantly throbbing with exaggerated ache when lifting the right arm or when ambulating, interferes with activities of daily living and quality of sleep.

Pain rating: 6/10 at rest, 8/10 with movement

Pain goals: 2/10, to be able to brush her hair and her teeth with minimal pain, wants to stay as alert as possible

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What is Pain?

- Medical Definition

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage"

International Association for the Study of Pain, 1979

- Operative Definition

"Pain is whatever the experiencing person says it is, existing whenever he/she says it does."

Margo McCaffery

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Types of Pain

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Types of Pain

Nociceptive

- Somatic: skin, tissue or musculoskeletal pain, often described as aching or sharp, worsens with movement
- Visceral: "organ pain", sensitive to stretching, ischemia and inflammation, often described as deep, lancinating, colicky or episodic
- Inflammatory: usually related to tissue injury, may be described as aching

Neuropathic

- Central: CNS lesions, e.g. stroke, spinal cord injury, multiple sclerosis, described as spasticity, weakness, or burning pain on one side
- Peripheral: peripheral nerve lesions, e.g. diabetic neuropathy, complication of cancer therapies, described as shooting, electrical, burning pain

Non-Physical

- "Existential Crisis"
- Spiritual, social, cultural, psychological, emotional
- Not typically relieved by treatment of physical symptoms

Thomas and Von Gunten, 2003.

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Pain Classifications

Acute Pain

- Identified event
- Resolves within days-weeks
- Usually nociceptive

Chronic Pain

- Multifactorial, cause not easily identified
- ≥ 3 months of persistent pain
- Nociceptive or neuropathic

Acute on Chronic Pain

- Incident pain
- Breakthrough pain

Dowell et al, 2016.

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Patient Case: Mrs. Amanda Anderson

Amanda describes her pain as constantly throbbing in her right arm pit and left hip, with an exaggerated ache when she lifts her arm or tries to ambulate.

What kind of pain is Amanda is experiencing?

- A. Neuropathic pain
- B. Visceral, inflammatory pain
- C. Somatic, inflammatory pain

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Amanda describes her pain as constantly throbbing in her right arm pit and left hip, with an exaggerated ache when she lifts her arm or tries to ambulate.

What kind of pain is Amanda is experiencing?

- A. Neuropathic pain
- B. Visceral, inflammatory pain
- C. **Somatic, inflammatory pain**

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Pain Assessment

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Cornerstones of effective pain management:

- »Thorough and frequent pain assessments
- »Consistent documentation

Perron and Schonwetter, 2001.
Ruder, 2010.

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Patient Assessment

Obtain medical and psychosocial history

- Identify barriers to successful pain management
- Evaluate current and previous treatments for pain
- Differentiate physical pain from non-physical pain

Complete a thorough evaluation

- Cognitive function
- Estimated prognosis
- Medication adherence
- Administration route-specific factors

Discuss patient's *goals and expectations*

- Achievable and documented
- Pain scores
- Sedation or other side effects
- Participation in activities

Oliver et al., 2008.
Ruder, 2010.

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Pain Assessment: PQRST

• **P**rovocation/Palliation

- What makes your pain better/worse?
- Is it worse with movement? Does it improve with rest?

• **Q**uality

- What words would you use to describe your pain?
 - Somatic pain → aching, sharp, worsens with movement
 - Visceral pain → deep, lancinating, episodic, colicky
 - Neuropathic pain → “pins and needles”, burning, shooting, electrical

• **R**egion/Radiation

- Where is your pain located? Is there more than one site?
 - Somatic, inflammatory pain is well-localized
 - Visceral pain is poorly localized
 - Neuropathic pain has a radiating quality

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Pain Assessment: PQRST

- **S**everity

- How severe is your pain right now on a scale of 1-10?
- How bad is it at its worst? Best?
- How has it interfered with your activities?
- How has it affected your sleep, relationships, mood, functionality?

- **T**ime/Temporal Relationship

- Onset of pain?
 - Has intensity worsened over time?
 - How often does it occur? Is it constant or intermittent?
 - How long does an episode last?
 - Is pain better/worse at certain times of the day?
 - How long does it take for your pain medicine to work? How long does the relief last?
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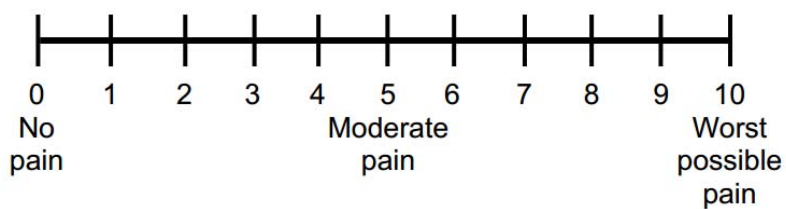
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Patient-Dictated Scales

Wong-Baker FACES® Pain Rating Scale



Numeric Pain Rating Scale



<http://www.wongbakerfaces.org/>
http://www.painedu.org/Downloads/NIPC/Pain_Assessment_Scales.pdf

Observational Scales: PAIN-AD

Items	0	1	2	Score
Breathing independent of vocalization	Normal	Occasional labored breathing. Short period of hyperventilation.	Noisy labored breathing. Long period of hyperventilation. Cheyne-Stokes respirations.	
Negative vocalization	None	Occasional moan or groan. Low-level speech with a negative or disapproving quality.	Repeated troubled calling out. Loud moaning or groaning. Crying.	
Facial expression	Smiling or inexpressive	Sad. Frightened. Frown.	Facial grimacing.	
Body language	Relaxed	Tense. Distressed pacing. Fidgeting.	Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out.	
Consolability	No need to console	Distracted or reassured by voice or touch.	Unable to console, distract or reassure.	
Total				

Warden, Hurley, Volicer. 2003.

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Observational Scales: FLACC

Item	Score		
	0	1	2
Face	No particular expression or smile	Occasional grimace, frown, withdrawn or disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, or tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, or tense	Arched, rigid, or jerking
Cry	No cry	Moans, whimpers, or occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

Voepel-Lewis et al, 2010.

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Patient Case: Mrs. Amanda Anderson

- Provocation/palliation – provoked by movement, palliated with rest
 - Quality – throbbing, aching
 - Region/radiation – no radiation, well localized under the arm and in left hip
 - Severity – fluctuates from 6-8/10, interferes with activities of daily living
 - Temporal relationship – previously intermittent, worsened in the last 48 hours, now constant

 - Goals: 2/10, to be able to brush hair, brush teeth and lift her arm to eat with minimal pain, to remain as alert as possible
 - History of analgesic use – ibuprofen (minimally effective), opioid naïve
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Non-Pharmacological Interventions

Lexi-Drugs Online, 2017.

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Non-Pharmacological Approaches

- Goal: reduce perception of pain
- Interventions:
 - Acupuncture
 - Art, music, aromatherapy or pet therapy
 - Distraction, guided imagery, relaxation
 - Environmental modification/familiar objects
 - Heat/cold therapy
 - Hypnosis
 - Massage therapy
 - Transcutaneous electrical stimulation (TENS)
- Ensure collateral symptoms are addressed
 - Insomnia, fatigue, loss of appetite, anxiety, depression

Fouladbakhsh et al, 2011.

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Pharmacotherapy: Non-Opioid Analgesics

Lexi-Drugs Online, 2017.

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Acetaminophen

- Analgesic with antipyretic properties, *not an anti-inflammatory*
 - Useful for mild somatic pain
- Availability
 - Oral: tablets, capsules, oral solution (160mg/5mL)
 - Rectal: suppositories
 - Intravenous: \$\$\$\$, weight-based dosing, administered undiluted over 15 minutes
- Dosing
 - 325-650mg orally or rectally q4-6h prn, or scheduled, (maximum daily dose: 4000mg in adults, 3000mg in geriatric patients, 2000mg with hepatic impairment)
- Adverse effects
 - Chronic daily dosing, and doses exceeding 4000mg/day can cause hepatotoxicity
 - May increase INR in patients on warfarin, limit to 2000mg/day on consecutive days

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Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

- Analgesic, antipyretic, anti-inflammatory properties
 - Mild-moderate somatic and visceral pain
 - Acute or chronic inflammatory/bone pain

Mixed COX 1 and 2 inhibitors	Oral	Ibuprofen: 200-800mg PO q4-8h prn or scheduled (max: 3200mg/day) Naproxen: 250-500mg PO q8-12h prn or scheduled (max: 1500mg/day) *Ketorolac: 20mg x1, followed by 10mg PO q4-6h prn (max: 40mg/day)
	Topical	Diclofenac cream, patch, gel, solution
	IV/IM	*Ketorolac 30mg q6h prn (max: 120mg/day, ≤ 5 days)
Preferential COX 2		Meloxicam: 7.5-15mg PO daily (max: 15mg/day)
Selective COX 2		Celecoxib 100-400mg PO once to twice daily (max: 400mg/day)

*Oral ketorolac is only intended to complete a course or parenteral ketorolac, 5 day limit

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NSAID Adverse Effects

- Geriatric patients at higher risk for adverse events
- Gastrointestinal bleeding
 - Selective/Preferential COX-2 inhibitors present a decreased risk
 - Risk factors: peptic ulcer disease, advanced age, prior NSAID complications, concurrent corticosteroid or anticoagulant use, high doses of NSAIDs
 - Prevention: proton pump inhibitors (e.g. omeprazole OTC), and H2 blockers (e.g. famotidine)
- All NSAIDs
 - Cardiovascular events (MI/stroke)
 - Renal toxicity – maintain adequate hydration
 - Inhibition of platelet aggregation – use cautiously in patients with bleeding disorders, or those taking anticoagulants
 - Fluid retention – may exacerbate hypertension and heart failure

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Pharmacotherapy: Adjuvant Agents

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Antidepressants

- Useful in the treatment of neuropathic pain

 - Tricyclic antidepressants (TCA)
 - Nortriptyline, desipramine, amitriptyline
 - Adverse effects: dry mouth, orthostatic hypotension, urinary hesitancy, fatigue, somnolence, confusion, exacerbation of conduction delays, falls

 - Serotonin/Norepinephrine Reuptake Inhibitor (SNRI)
 - Duloxetine
 - Adverse effects: headache, fatigue, nausea, weakness
 - Venlafaxine
 - Adverse effects: insomnia, diaphoresis, nervousness, nausea
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Antidepressants

Medication	Adult Starting Dose (PO)	Titration Process	Max Daily Dose
Nortriptyline (Pamelor®)	25mg qhs	All TCAs: Increase by 25mg/day every 3-7 days as tolerated; dosed once daily at bedtime	150mg
Amitriptyline (Elavil®)	25mg qhs		150mg
Desipramine (Norpramin®)	25mg qhs		150mg
Duloxetine (Cymbalta®)	30mg daily	Increase to 60mg once daily after 7 days	60mg
Venlafaxine ER (Effexor XR®)	37.5mg daily	Increase by 75mg each week to a maximum of 225mg daily	

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Anticonvulsants

- Useful in the treatment of neuropathic pain
- Adverse Effects
 - sedation, dizziness, nausea/GI upset, confusion, tremors, memory loss, decreased coordination, decreased concentration, nystagmus

Medication	Adult Starting Dose (PO)	Titration Process	Max Daily Dose
Gabapentin (Neurontin®)	100mg qhs (geriatric) 300mg qhs (adult)	Increase by 100mg or 300mg doses every 3-7 days as tolerated; Dosed tid	3600mg; Reduce if renal impairment
Pregabalin (Lyrica®)	50mg bid	Increase by 100mg/day every 3-7 days as tolerated	600mg; Reduce if renal impairment
Carbamazepine (Tegretol®)	100-200mg bid	Increase by 200mg/day as tolerated, usual dose 200-400mg bid to qid	1200mg/day

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Topical Lidocaine

- Useful for diabetic neuropathy
 - Lidocaine 4% or 5% cream (OTC): apply up to 4 times daily
 - Lidocaine 4% patches (OTC): 12 hours on, 12 hours off
 - Lidocaine 5% patches (Rx): 12 hours on, 12 hours off (\$\$\$\$)
- Useful for oropharyngeal pain
 - Lidocaine 2% viscous solution, 15 mL swish/spit q4h prn
 - If lidocaine is swallowed, wait 30 min before eating/drinking
- Useful for wound care
 - Lidocaine 2% viscous solution, apply to wound during dressing changes

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Corticosteroids

- Anti-inflammatory, anti-emetic, appetite stimulant & mood stimulant properties
 - Useful in treatment of visceral pain (capsular, stretching), and somatic pain (bone)
 - Dexamethasone penetrates CNS and bone tissue more effectively than prednisone
- Dosing Pearls
 - Prednisone 10-20mg po daily or bid
 - Dexamethasone 2-16mg po daily or bid
 - Dose equivalency: prednisone 5mg = dexamethasone 0.75mg
 - Administering in divided doses can reduce GI upset
 - Give second dose early in the afternoon to minimize insomnia
- Adverse Effects
 - Hyperglycemia, gastric irritation or bleed, hypertension, adrenal insufficiency, psychosis (rare), edema (prednisone)
 - Hyperglycemia: tight glycemic control may no longer be necessary. Blood glucose goal between 200-250mg/dL typically sufficient for symptom control.

Jeffreys and Rosielle, 2012.
Tice, 2006.

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Antispasmodics, Benzodiazepines and Muscle Relaxers

- **Antispasmodic** – abdominal/colicky pain
 - Hyoscyamine 0.125-0.25mg SL q4h prn
 - Helpful for managing pain and nausea secondary to bowel obstruction
 - Adverse effects: confusion, drowsiness, fatigue, urinary retention
- **Benzodiazepine** – muscle spasms
 - Lorazepam: 0.5-2mg po 3-4 times daily
 - Diazepam: 2-10mg po 3-4 times daily
 - Long half-life, poorly tolerated in the elderly and those with renal impairment
 - Adverse effects: drowsiness, confusion, fatigue, slurred speech, dizziness
- **Muscle relaxer** – muscle spasms
 - Baclofen: 5-20mg po tid
 - Adverse effects: drowsiness, confusion, nausea, hypotension
 - Cyclobenzaprine: 5-10mg po tid
 - TCA-like structure, poorly tolerated in the elderly

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Place in Therapy

Neuropathic Pain	<ul style="list-style-type: none"> • Antidepressants → nortriptyline, duloxetine • Anticonvulsants → carbamazepine, gabapentin, pregabalin • Topical agents → lidocaine
Inflammatory/ Bone Pain	<ul style="list-style-type: none"> • Corticosteroids → dexamethasone, prednisone
Visceral or Colicky Pain	<ul style="list-style-type: none"> • Antispasmodics → hyoscyamine • Corticosteroids for capsular/stretching pain
Muscle Spasms	<ul style="list-style-type: none"> • Benzodiazepines → lorazepam, diazepam • Muscle relaxers → baclofen, cyclobenzaprine

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Patient Case: Mrs. Amanda Anderson

Amanda's provider suspects lymph and bone metastases are contributing to the inflammatory pain in her right arm and left hip, and would like to start a new analgesic regimen to replace the ibuprofen which has been minimally effective. Amanda has declined use of an opioid at this time, as she wants to remain as alert as possible in order to help care for her children.

Which regimen would you recommend?

- A. Topical lidocaine applied 3 times daily
- B. Dexamethasone 4 mg po twice daily
- C. Nortriptyline 25mg po qhs
- D. Gabapentin 300mg po qhs

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Pharmacotherapy: Opioids

Lexi-Drugs Online, 2017.

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Clinical Pearls

- Opioids can be used to manage:
 - Nociceptive pain
 - Neuropathic pain (methadone)
 - “Air hunger”

- Individual variations
 - Genetic variability in number and distribution of opioid receptors
 - Accounts for differences in effectiveness and side effects of opioids

Protus et al, 2015.

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Opioid Classification: Agonists

Phenanthrenes

- ✘ Codeine: Tylenol® #3, #4
- Morphine: MS Contin®, Roxanol®
- Hydrocodone: Vicodin®, Lortab®, Norco®, Zohydro ER®
- Hydromorphone: Dilaudid®, Exalgo®
- Oxycodone: OxyContin®, Percocet®
- Oxymorphone: Opana®
- Buprenorphine (Butrans®, partial agonist)

Diphenylheptanes

- Methadone

Phenylpiperidines

- Fentanyl: Duragesic®
- ✘ Meperidine: Demerol®

Miscellaneous

- Tapentadol (Nucynta®)
- Tramadol (Ultram®)

✘ = Not recommended for pain

Protus et al, 2015.
Miller et al, 2001.

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Opioid Selection and Rotations

Factors impacting initial selection

- History of opioid use/intolerance
- Dosage form limitations
- Renal/hepatic impairment
- Patient goals/preferences
- Availability
- Cost

Factors impacting opioid rotation

- Lack of therapeutic response
- Intolerable side effects
- Change in patient status
 - Inability to use specific dosage formulations
 - Moving inpatient ↔ outpatient
 - New onset renal/hepatic impairment

Miller et al, 2001.

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Preferred Opioids for Hospice & Palliative Care

Opioid	Routes of Administration	Preferred Formulations
Morphine	PO, SL, PR, IV, SC	ER capsules 24H, ER tablets 12H, IR tablets, oral solution, injectable, suppositories
Hydromorphone	PO, SL, PR, IV, SC	IR tablets, oral solution, injectable, suppositories
Oxymorphone	PO, PR, IV, SC	ER tablets (12H), IR tablets, Injectable
Oxycodone	PO, SL, PR	IR capsule, IR tablet, oral solution, oral concentrate IR Combinations with acetaminophen, aspirin, ibuprofen, naloxone, naltrexone
Hydrocodone	PO	IR Combinations with acetaminophen, ibuprofen, antitussives
Methadone	PO, SL, PR, IV, SC	Oral concentrate, injectable, tablet
Fentanyl	SL, IV, SC, Transdermal, Intranasal	ER – transdermal patches IR – oral spray, lozenge, nasal spray, sublingual/buccal tablets, injectable

PO: Oral, SL: Sublingual, PR: Rectal, IV: Intravenous, SQ: Subcutaneous, 24H: Q24H dosing, 12H: Q12H dosing
Abuse-deterrent formulations available for Morphine ER, Hydromorphone ER, Oxymorphone ER, Oxycodone IR/ER, Hydrocodone ER; should be swallowed whole – do not give SL or PR

Protus et al, 2015.

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Opioid Agonists: Morphine

- World Health Organization opioid of choice
 - Available in multiple dosage forms
 - Immediate-release liquid (20mg/mL) and tablets
 - Sustained release (SR) tablets can be dosed every 8 to 12 hours
 - SR pellets in capsules can be dosed once every 24 hours (e.g. Kadian®)
 - Injectable
 - Metabolized in the liver to morphine-3-glucuronide (no analgesic effect, neurotoxic) and morphine-6-glucuronide (active metabolite, analgesic effect)
 - Kidneys eliminate toxic morphine metabolite
 - Use with extreme caution in patients with renal impairment, unable to eliminate this metabolite effectively
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Opioid Agonists: Hydromorphone, Hydrocodone

- Hydromorphone
 - Available in multiple dosage forms for PO, SL, IV/IM/SC
 - IR and ER formulations available, IR tablets can be administered PR
 - Less neurotoxic compared to morphine
 - Potent injectable is useful for SC administration (10mg/ml)
 - Hydrocodone
 - Available for **PO** use as extended release (ER) product (example: Zohydro ER®), and immediate release (IR) product in combination with other agents (acetaminophen, ibuprofen, and multiple antitussives)
 - Dosing limitations exist for combination products
 - Metabolized to hydromorphone in the liver, avoid in patients with hepatic impairment
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Opioid Agonists: Oxycodone, Oxymorphone

- Oxycodone
 - May be a suitable alternative to morphine in patients with renal impairment, or those unable to tolerate morphine due to side effects
 - May administer IR tablets rectally, *unless using abuse-deterrent form*
 - Oral concentrate (20mg/ml) is not cost-effective, IR tabs can be crushed and given SL
 - Use cautiously in patients with hepatic impairment
 - Ceiling doses on combination products

 - Oxymorphone
 - Active metabolite of oxycodone
 - Oral IR and ER formulations available
 - Contraindicated for use in moderate to severe hepatic impairment
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Fentanyl

- Transdermal Patch (Duragesic®)
 - Initial effects seen within 24 hours, maximum effects seen within 2-3 days of initiation
 - Potentially altered absorption if patient is dehydrated, cachectic or losing weight
 - Reserve the use of transdermal fentanyl for patients who are *opioid tolerant* (taking the equivalent of morphine 60mg/day for ≥ 7 days)

 - Injection (IV/SC)
 - Onset of action within minutes
 - Duration of activity 30-60 minutes

 - Rapid onset products
 - Transmucosal, buccal tablet, intranasal, sublingual tablet, sublingual spray
 - These products are not interchangeable and are very expensive
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Methadone

- Advantages
 - Tablets can be crushed, excellent for neuropathic pain, generally better tolerated compared to other opioids
- Limitations
 - Variable response, drug-drug interactions, potential for arrhythmias
- Pharmacokinetics
 - Half life range 5-130 hours (average 20-35), onset 30-60 minutes, peak 4 hours
 - Duration of effect increases with repeated dosing, reaches steady state within 3-7 days
- Key Points
 - Wait 3-7 days before titrating dose again, due to prolonged time to reach steady state,
 - Monitor patient closely for first 5 days (opioid toxicity, cardiotoxicity)

Protus et al, 2015.
Ferrari et al, 2004.

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Methadone: Who is a good candidate?



Consider methadone

- Neuropathic pain
- Need a crushable/liquid long-acting opioid
- Neurotoxicity from other opioids
- Renal insufficiency
- Allergies to multiple opioids
- Intolerable side effects from other opioids
- Cost of opioid therapy is a barrier to effective pain control



Possibly avoid methadone

- Known cardiac arrhythmia/bradycardia
- Electrolyte imbalances (*hypokalemia*)
- Acute pain crisis
- Rapid titration of analgesia is necessary
- Unable to monitor use
- Unreliable caregiving situation
- Patient taking multiple interacting medications
- Prognosis limited to < 1 week

Consult a skilled clinician prior to initiating methadone

Protus et al, 2015.
Gazelle and Fine, 2003.

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Partial Opioid Agonists: Tramadol (Ultram®)

- Opioid agonist and norepinephrine and serotonin reuptake inhibitor
 - Major metabolite is a weak mu opioid receptor agonist
- Dose
 - Immediate release: 50-100mg q4-6hrs (Max 400mg/day)
 - Extended release: 100mg once daily (Max 300mg/day)
- Adverse effects
 - Dizziness, somnolence, constipation, nausea, confusion
 - Precautions/contraindications: history of seizures, concurrent serotonergic agents (serotonin syndrome), renal impairment, hepatic impairment

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Partial Opioid Agonists: Tapentadol (Nucynta®)

- Opioid agonist and norepinephrine reuptake inhibitor
- Dose
 - Immediate release: 50-100mg every 4-6 hours (Max: 600mg/day)
 - Extended release: 50mg BID, titrate by 50mg BID every 3 days (Max: 500mg/day)
 - Do not crush, break or chew ER product
- Adverse Effects
 - Dizziness, somnolence, constipation, nausea, confusion
 - Precautions/contraindications: Pulmonary function impairment, severe renal impairment, severe hepatic impairment, history of seizures

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Partial Opioid Agonists: Buprenorphine (Butrans®)

- Partial opioid agonist
 - Partial mu agonist and weak kappa antagonist activity

 - Ceiling dose
 - Behaves like an antagonist at higher doses

 - Patch
 - Applied once weekly for management of moderate to severe chronic pain
 - Available as 5mcg/hr, 10mcg/hr, 20mcg/hr patch
 - 20mcg patch ~ 50mg/day oral morphine

 - May precipitate withdrawal in opioid-dependent patients taking higher than 50mg/day of oral morphine equivalents
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Opioid Routes of Administration

- The timing of opioid administration depends on
 - The route of administration
 - Onset of effect
 - Duration of activity

Common Routes	Onset of Effect	Duration of Activity
Oral	30-90 minutes	IR = 3-4 hours ER = 8-24 hours
Sublingual	3-5 minutes	3-4 hours
Rectal	5-30 minutes	Variable
Intravenous	1-2 minutes	30-60 minutes
Subcutaneous	15-30 minutes	1-2 hours

Miller et al, 2001.
Walsh et al, 2004.

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Opioid Use in Renal and Liver Failure

	Preferred	Consider	Avoid
Hepatic Failure	Hydromorphone Methadone Morphine	Fentanyl Oxycodone	Codeine Hydrocodone Tramadol
Renal Failure	Fentanyl Methadone	Hydrocodone Hydromorphone Oxycodone	Codeine Morphine Tramadol
Hepatic and Renal Failure	Hydromorphone Methadone	Fentanyl Oxycodone	Codeine Hydrocodone Morphine Tramadol

Johnson, 2007.

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Patient Case: Mrs. Amanda Anderson

Dexamethasone was tapered to 4mg po qam as Amanda's blood glucose values were regularly exceeding 250mg/dL. She would like to remain on dexamethasone as she finds it helpful for her fatigue and mood, but unfortunately pain control worsened with dexamethasone taper. Patient is now prepared to try a low dose opioid for pain. Her primary provider notes evidence of liver involvement at this time, and would like a recommendation for an opioid that is safe to use in liver disease.

Which opioid would you recommend?

- A. Morphine 5mg po q2h prn
- B. Codeine 30mg po q6h prn
- C. Hydrocodone/acetaminophen 10/325 1 tab po q4h prn
- D. Tramadol 25mg po q6h prn

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What about her codeine allergy?

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Opioid Allergies

- Anaphylactic opioid allergies are the only *true* opioid allergies
- What about pruritus or urticaria following morphine use?
 - Pseudo-allergy: reaction following first dose of morphine
 - True allergy: reaction following a previous exposure to morphine (requires sensitization)

Phenanthrenes	Buprenorphine, codeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone
Phenylpiperadines	Fentanyl, meperidine
Diphenylheptanes	Methadone
Phenylpropylamines	Tapentadol, tramadol

Zhang et al. 2018.

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Opioid Adverse Effects

Lexi-Drugs Online, 2017.

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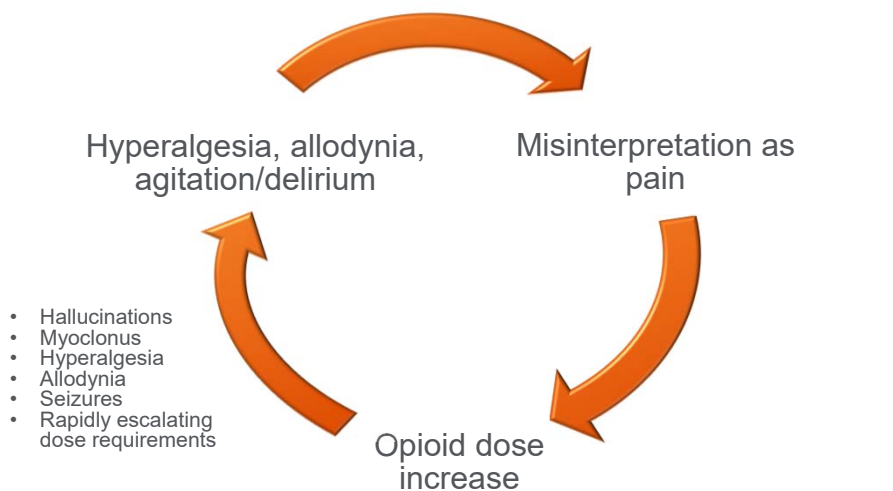
Treating Opioid Adverse Effects

Common	Severe/Less Common
<ul style="list-style-type: none"> • Constipation <ul style="list-style-type: none"> – Senna-S, bisacodyl, methylnaltrexone • Dry Mouth <ul style="list-style-type: none"> – Hard candy – ↓ dose • Nausea/vomiting <ul style="list-style-type: none"> – Prochlorperazine, haloperidol – ↓ dose • Fatigue <ul style="list-style-type: none"> – Methylphenidate, corticosteroid – ↓ dose • Sweats <ul style="list-style-type: none"> – ↓ dose 	<ul style="list-style-type: none"> • Pruritus/urticaria <ul style="list-style-type: none"> – Rotate opioid – Diphenhydramine, ranitidine • Bad dreams/hallucinations <ul style="list-style-type: none"> – Rotate opioid – ↓ dose • Dysphoria/delirium <ul style="list-style-type: none"> – Rotate opioid – ↓ dose • Myoclonus/seizures <ul style="list-style-type: none"> – Rotate opioid – Consider benzodiazepine • Respiratory depression <ul style="list-style-type: none"> – Hold and/or ↓ dose

Martin and Forrester, 2013.

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Opioid Induced Neurotoxicity (OIN)



Chu, Angst, Clark. 2008.

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Opioid-Induced Neurotoxicity

- Can occur with ALL opioids at high doses
- Incidence varies by opioid
Morphine > Hydromorphone > Oxycodone > Fentanyl > Methadone
- Risk factors:
 - Renal impairment, rapid dose escalation, dehydration, underlying delirium, advanced age, other psychoactive medications (benzodiazepines, tricyclic antidepressants)
- Early recognition is critical
- Treatment → Opioid dose reduction +/- Opioid rotation

Vorobeychik, 2008.

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Key Factors for Achieving Good Pain Control

- Assess nature of the pain by completing a thorough assessment
- Identify type of pain
- Evaluate efficacy of current pain regimen
- Help patient set achievable goals for pain relief
- Select the appropriate analgesic based on type of pain, and patient-specific factors that would drive drug selection
- Perform ongoing assessments and document findings thoroughly and consistently

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Dyspnea

Underlying Causes
Clinical characteristics
Treatment

Dyspnea

- Dyspnea is a self-reported, subjective, distressing, sense of breathlessness
- Approximately 70% of hospice patients will experience dyspnea
- Respiratory rate and other objective findings often do not correlate with patient's perception of dyspnea

Shadd et al.
Protus, et al.

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Dyspnea

- Non-reversible causes
 - Airway obstruction (COPD, tumor burden)
 - Cardiac: heart failure, pulmonary hypertension
 - Muscle weakness: amyotrophic lateral sclerosis (ALS), multiple sclerosis, cachexia
 - Parenchymal failure: cystic fibrosis, pneumonia, pulmonary fibrosis
 - Reversible causes
 - Bronchospasm secondary to pulmonary disease
 - Fluid overload secondary to heart/liver failure
 - Hypoxia
 - Anxiety
 - Pain
-

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Dyspnea: Non-Pharmacological Approaches

- Goal is to decrease the perception of breathlessness
- Interventions
 - Deep, slow breathing into a paper bag
 - Improve air circulation using a fan
 - Maintain cool room temperature
 - Reposition for comfort
 - Minimize triggers
 - Focus on relaxation
 - Provide companionship



Image: www.cafepress.com.

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Pharmacological Interventions: Pulmonary Disease

Lexi-Drugs Online, 2017.

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Dyspnea secondary to COPD

- Pharmacological therapy
 - Bronchodilators (inhaled, nebulized)
 - Relax smooth muscle around airways
 - Inhaled or nebulized
 - Anticholinergics
 - Prevent muscles around airways from tightening
 - Inhaled or nebulized
 - Corticosteroids
 - Decreasing inflammation leads to less swelling and mucus production in the airways
 - Inhaled, nebulized, or taken orally

 - Take Note!
 - Nebulized medications are generally preferred for patients with advanced COPD who lack the lung capacity to use inhalers properly and effectively
-

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Take Note!

- Patients with advanced COPD may lack the capacity to use inhalers effectively
 - Inappropriate use of inhalers can lead to increased systemic side effects
 - Switch to nebulized medications if needed

 - Inhaled corticosteroids can cause thrush
 - Rinse mouth out with water following each use
 - Switch to oral corticosteroids if thrush recurs
-

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Pharmacological Therapy: Bronchodilators

Generic (Trade Name)	Adult Starting Dose	Routes of Administration	Comments
Albuterol (AccuNeb®)	2.5mg Q4H PRN MDI: 2 puffs Q4H PRN	Inhalation via nebulizer or meter dose inhaler (MDI)	Short acting beta-agonist
Levalbuterol (Xopenex®)	0.63mg Q6H PRN MDI: 2 puffs Q6H PRN	Inhalation via nebulizer or MDI	Short acting beta-agonist
Arformoterol (Brovana®)	15mcg BID	Inhalation via nebulizer	Long acting beta-agonist
Formoterol (Perforomist®)	20mcg BID	Inhalation via nebulizer	Long acting beta-agonist
Salmeterol (Serevent®)	50mcg BID	Inhalation via dry powder inhaler	Long acting beta-agonist

Pharmacological Therapy: Anticholinergics

Generic (Trade Name)	Adult Starting Dose	Routes of Administration	Comments
Ipratropium (Atrovent®)	500mcg Q6-8H MDI: 2 puffs QID	Inhalation via nebulizer or MDI	Short acting anticholinergic
Tiotropium (Spiriva®)	18mcg QD MDI: 2 puffs QD	Inhalation via dry powder inhaler or MDI	Long acting anticholinergic
Umeclidinium (Incruse Ellipta®)	62.5mcg QD	Inhalation via dry powder inhaler	Long acting anticholinergic
Aclidinium (Tudorza Pressair®)	400mcg BID	Inhalation via dry powder inhaler	Long acting anticholinergic

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Pharmacological Therapy: Corticosteroids

Generic (Trade Name)	Adult Starting Dose	Routes of Administration	Comments
Prednisone (Deltasone®)	10mg QD	PO	Risk for peripheral edema Dose early in the day
Dexamethasone (Decadron®)	2-4mg QD	PO/PR/SC/IV/IM	Less risk for peripheral edema Dose early in the day
Budesonide (Pulmicort®)	2mg BID-QID 100-400mcg QD	Inhalation via nebulizer or dry powder inhaler	Risk for oral thrush
Fluticasone (Flovent®)	50-500mcg QD	Inhalation via dry powder inhaler or MDI	Risk for oral thrush

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Pharmacological Therapy: Combo Inhalers

Generic (Trade Name)	Adult Starting Dose	Routes of Administration	Comments
Ipratropium/ albuterol (Combivent®, Duoneb®)	500mcg/2.5mg QID MDI: 1 puff QID	Inhalation via nebulizer or MDI	Short acting anticholinergic + Short acting beta-agonist
Umeclidinium/ Vilanterol (Anoro Ellipta®)	1 puff QD	Inhalation via dry powder inhaler	Long acting anticholinergic + Long acting beta-agonist
Budesonide/ Formoterol (Symbicort®)	2 puffs BID	Inhalation via MDI	Inhaled steroid + Long acting beta-agonist
Fluticasone/ Salmeterol (Advair®)	1 puff BID	Inhalation via dry powder inhaler or MDI	Inhaled steroid + Long acting beta-agonist
Fluticasone/ Vilanterol (Breo Ellipta®)	1 puff QD	Inhalation via dry powder inhaler	Inhaled steroid + Long-acting beta agonist

Take Note!

Most patients on combination inhalers can be switched to routine albuterol/ipratropium nebulizer treatments up to q4h, along with an oral corticosteroid such as prednisone.

Question

- 82 y/o male with advanced COPD complains of dyspnea. Patient has not been able to use his inhalers properly, and recently had thrush. Patient prefers to avoid opioids and benzodiazepines.
 - Current Medications: Atrovent® 2 puffs QID, Proair® 2 puffs q4h prn, Flovent® 2 puffs BID
 - What action is the most appropriate intervention?
 - A. Change inhalers to nebulizer form, and replace inhaled steroid with an oral steroid
 - B. Change inhaled steroid to nebulized steroid
 - C. Change anticholinergic inhaler to nebulized long-acting beta agonist
 - D. Start morphine (Roxanol®) for dyspnea as needed
-

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Pharmacological Interventions: Fluid Overload

Lexi-Drugs Online, 2017.

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Underlying Causes

- Pulmonary Congestion
 - Due to organ failure, infection, inflammation
 - Treat with non-pharmacological interventions, diuretics

 - Ascites
 - Due to liver failure or malignancy
 - Treat with paracentesis, diuretics

 - Lymphedema
 - Due to lymphatic system failure
 - Treat with lymphatic massage
-

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Non-Pharmacological Therapy

- Pulmonary Congestion
 - Reposition to comfort
 - Sleep at an incline

 - Paracentesis
 - For patients with intolerable ascites
 - Patients generally tolerate small volume paracentesis (1-2 liters) well
 - Permanent drains or shunts can be considered for patients with longer prognosis

 - Lymphatic massage
 - Performed by trained massage therapists and physical therapists
 - Generally begin centrally in neck or trunk area to clear our main lymphatic pathways
-

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Pharmacological Therapy

- Diuretics:
 - Limited/no benefit in lymphedema
 - Avoid in dehydrated patients

 - Risks with diuretics:
 - Electrolyte disturbances
 - Orthostatic hypotension
 - Hypotension
 - Dehydration
-

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Pharmacological Therapy

Generic (Trade Name)	Adult Starting Dose	Routes of Administration	Loop Diuretic Equivalent Dose
Furosemide (Lasix®)	20mg QD	PO/SL/PR/SC/IM /IV	40mg (Lasix® IV dose is equal to ½ PO dose)
Bumetanide (Bumex®)	0.5mg QD	PO/IV/IM	1mg (Bumex® IV to PO dose is the same)
Torsemide (Demadex®)	10mg QD	PO	20mg

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Pharmacological Therapy

Generic (Trade Name)	Adult Starting Dose	Routes of Administration	Comments
Metolazone (Zaroxolyn®)	2.5mg QD or PRN	PO	Thiazide diuretic
Hydrochlorothiazide (Microzide®)	25mg QD	PO	Thiazide diuretic Ineffective with CrCl<30ml/min
Spironolactone (Aldactone®)	25mg QD	PO	Potassium sparing diuretic 40mg:100mg ratio with Lasix®

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Question

- 78 y/o male with hospice diagnosis of CHF complains of shortness of breath.
 - Assessment: 2+ pitting edema, BP 89/60 HR 87
 - Current Medications: Tylenol® 500mg q4h prn, Lasix® 80mg daily, K-Tab® 20meq daily, Celexa® 20mg daily, Norvasc® 10mg daily
- What action is the most appropriate intervention?
 - A. Initiate comfort medications for dyspnea
 - B. Add metolazone (Zaroxolyn®) 2.5mg daily as needed
 - C. Suggest sleeping at an incline
 - D. Both A & C

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Pharmacological Interventions: Hypoxia, anxiety & pain

Lexi-Drugs Online, 2017.

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Hypoxia, Anxiety, Pain

- Symptomatic hypoxia: add supplemental oxygen (?)

- Anxiety: add a benzodiazepine
 - Lorazepam preferred in hospice due to versatility
 - Lorazepam 0.25-0.5mg PO/SL/PR/IV every 4 hours as needed

- Pain: consider using opioids
 - Opioids can also be used in the absence of pain
 - Suppress respiratory awareness, decrease hypoxia/hypercapnia response
 - Goal is not to suppress respiratory drive
 - Morphine (20mg/ml) 2.5-5mg PO/SL every 4 hours as needed

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Pharmacological Therapy: Opioids

Generic (Trade Name)	Adult PO Starting Dose	Comments
Morphine (Roxanol®)	2.5-5mg Q4H PRN	Monitor for signs of neurotoxicity in renal impairment
Hydromorphone (Dilaudid®)	2mg Q4H PRN	Monitor for signs of neurotoxicity in renal impairment
Oxycodone (Roxicodone®, OxyFast®)	2.5-5mg Q4H PRN	Preferred in patients with renal failure

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Pharmacological Therapy: Benzodiazepines

Generic (Trade Name)	Adult Starting Dose	Routes of Administration	Approximate Equivalent Dosing
Alprazolam (Xanax®)	0.25mg TID PRN	PO/SL/PR	0.5mg
Lorazepam (Ativan®)	0.5mg Q4H PRN	PO/SL/PR/SC/IM/IV	1mg
Clonazepam (Klonopin®)	0.25mg BID PRN	PO/SL/PR	0.25mg
Diazepam (Valium®)	2mg TID PRN	PO/SL/PR/IM/IV	5mg

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Nebulized Treatments for Refractory Dyspnea

Generic (Trade Name)	Adult Starting Dose	Routes of Administration	Comments
Sodium chloride 0.9% (saline nebulization solution)	3ml Q4H PRN	Inhalation	Benefit with thick secretions
Furosemide (Lasix®)	20mg QID	Inhalation	Dilute with 2ml 0.9% NS and administer via nebulizer
Fentanyl (Sublimaze®)	25mcg Q2H PRN	Inhalation	Dilute with 2ml 0.9% NS and administer via nebulizer

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Patient Case: Mrs. Amanda Anderson

- Refresher: 45 year old female admitted to hospice with recurrent breast cancer and lung metastases. Lymph and bone metastases suspected.
- Amanda presents with swelling in her right arm. This has been bothersome for Amanda. She indicates this swelling has occurred in the past and she is anxious about it progressing, as she remembers it being painful. Her husband was trained in lymphatic massage last year by a certified physical therapist to assist with lymphedema therapy at home.
- She denies shortness of breath.

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Patient Case- Mrs. Amanda Anderson

What action is the most appropriate intervention?

- A. Start nebulized fentanyl in anticipation of dyspnea
- B. Increase morphine as tolerated for pain and dyspnea, and add albuterol (AccuNeb®) via nebulizer q4h prn in anticipation of dyspnea
- C. Increase morphine as tolerated for pain, and initiate lymphatic massage (or manual lymph drainage)
- D. Start furosemide (Lasix®) 20mg daily for lymphedema

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Key Factors for Optimal Management of Dyspnea

- Optimal efficacy will be achieved by targeting the underlying cause (may be multifactorial)
- Goal of therapy is to decrease the patient's perception of dyspnea
- COPD
 - Assess ability to properly use inhalers, avoid overuse of bronchodilators
- Fluid overload
 - Treat with diuretics as blood pressure and hydration status allows

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Questions?

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