Important Medications in Palliative Care: A Primer

Goals of this presentation:

- Understand the importance of pharmacotherapy in palliative care and its history in medicine
- Explain the key terminology and concept differences between palliative care, comfort care, and hospice
- Outline key medications or medication classes used for treatment of common palliative care symptoms
- Review basic principles of opioid equianalgesic dose conversion
- Discuss polypharmacy, potentially inappropriate medications, and deprescribing in palliative care
Palliative Care

A brief history

- Palliative care began with a focus on the care of dying

- It was described by Dame Cicely Saunders in the early 1950’s that only an interdisciplinary team could relieve the “total pain” of a dying person in the context of his or her family

- The team concept is at the core of palliative care

- In 1974, Dr. Balfour Mount, a surgical oncologist at The Royal Victoria Hospital of McGill University in Montreal, Canada, coined the term palliative care to avoid the negative connotations of the word hospice in French culture, and introduced Dr. Saunders’ innovations into academic teaching hospitals

- 2006 – American Board of Medical Specialties recognized the subspecialty of Hospice and Palliative Medicine

- American Academy of Hospice and Palliative Medicine now has over 5,000 members globally
Definitions

<table>
<thead>
<tr>
<th>Palliative care</th>
<th>Hospice</th>
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</thead>
<tbody>
<tr>
<td>Philosophy</td>
<td>Medicare Benefit / human right</td>
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<tr>
<td>Holistic approach to care</td>
<td>Holistic approach to care</td>
</tr>
<tr>
<td>Use alongside curative intent</td>
<td>End of life</td>
</tr>
<tr>
<td>“All” therapies</td>
<td>Limited therapies (de-escalate fluids, blood products, etc)</td>
</tr>
</tbody>
</table>

Disease Progression

- Life Prolonging Care
- Palliative Care
- Hospice Care

Diagnosis of serious illness ➔ Death

What palliative care is not.

Palliative care study – increased PTSD with “drive-by style” palliative consults
### Symptom/Goal Directed Care

#### Symptoms/Syndromes

<table>
<thead>
<tr>
<th>Symptom/Syndrome</th>
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<tbody>
<tr>
<td>Anorexia/Cachexia</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Chronic cough</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Delirium (terminal agitation)</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Dysphagia</td>
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<tr>
<td>Dyspnea</td>
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<tr>
<td>Falls</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Hiccups</td>
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<tr>
<td>Hyperalgesia</td>
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<tr>
<td>Infections at the end-of-life</td>
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<tr>
<td>Insomnia</td>
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<tr>
<td>Mucositis/esophagitis</td>
</tr>
<tr>
<td>Myoclonus</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Pain (somatic, neuropathic, visceral, mixed, bone pain)</td>
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<tr>
<td>Polypharmacy</td>
</tr>
<tr>
<td>Pruritus</td>
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<tr>
<td>Respiratory tract secretions/death rattle</td>
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<tr>
<td>Sarcopenia</td>
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<tr>
<td>Small bowel obstruction (SBO)</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Vertigo/dizziness</td>
</tr>
<tr>
<td>Vomiting</td>
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<tr>
<td>Xerostomia</td>
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</table>

#### Dyspnea/breathlessness

**Subjective sensation of difficulty breathing**

**Causes of dyspnea at the EOL:**
- Anemia, anxiety, severe heart or lung disease, tumor compression, constipation, urinary retention

**Assessment:**
- Patient evaluation – oxygen tubing kinked or turned off inadvertently, fluid overload from IV fluids or TPN, pneumothorax, pleural effusions, pulmonary embolism
- Other uncontrolled symptoms (anxiety, pain, constipation, urinary retention)

**Reversible vs irreversible causes**

**Non-pharmacologic management (always optimize):**
- Positioning (sitting up, adjusting body position for more natural airflow)
  - Tri-pod position
  - Modification of activity level
  - Oxygen
  - Air movement – fan or open window; pursed lip breathing
- Bedside relaxation techniques (guided imagery, purposeful breathing)
- Discontinue IV fluids/TPN (if appropriate based on patient/family goals)

[https://www.mypcnnow.org/blank-mbri1](https://www.mypcnnow.org/blank-mbri1)
Studies of supplemental oxygen for relief of dyspnea have shown mixed results in hypoxemic patients with cancer and severe lung disease. Therapeutic trial is based on symptom relief, not pulse oximetry. Not always indicated or effective. Studies from 1992 to 2003:
- Advanced cancer, cardiac failure, and kyphoscoliosis
- Compared oxygen vs air inhalation
- No benefit of oxygen – number of patients was small in each study

Considerations:
- Vehicle to delivery oxygen – nasal cannula vs noninvasive ventilation
  - Noisy, uncomfortable, frightening
  - Delirium inducing
  - Aspiration risk
- Short term trial vs home therapy (cost considerations)

Oxygen? “Placebo vs medical symbolism vs benefit”

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 bronchoconstriction
- Stimulation of facial, nasal or pharyngeal receptors
- Increased capacity for exercise training
- Placebo effect

Dyspnea/breathlessness – Medications

- Pharmacologic management:
  - **Best for dyspnea at rest**
  - **Opioids** – drug of choice for dyspnea at the EOL/refractory dyspnea
    - Morphine 5-10 mg by mouth every 30 mins to 1 hour as needed
    - Morphine 2-4 mg IV by mouth every 10 mins to 1 hour as needed
  - May also use long acting therapies – 10-20 mg morphine ER daily
  - Terminal extubation (q10mins) vs relatively “comfortable” patient (q1hour)

Mechanisms by which opioids may reduce dyspnea

- Decreased metabolic rate and ventilatory requirements
- Reduced medullary sensitivity to hypercarbia or hypoxia
- Blunted medullary response to hypercarbia or hypoxia
- Alteration of neurotransmission within medullary respiratory centre
- Cortical sedation (suppression of respiratory awareness)
- Analgesia - reduction of pain-induced respiratory drive
- Anxiolytic effects
- Blunted afferent transmission from pulmonary mechanoreceptor to the CNS
- Vasodilation (improved cardiac function)
Opioids, dyspnea, and respiratory depression?

Common questions:

• Do patients with dyspnea have an increased risk of respiratory depression when getting opioids?  
  NO

• Is there an increase in mortality associated with the use of opioids for dyspnea?  
  NO

• Is there a benefit of nebulized opioids?  
  • Maybe – not enough evidence to recommend routinely  
  • Inhaled morphine or fentanyl


Dyspnea/breathlessness – Medications

Other agents:

• Corticosteroids - dexamethasone  
• Anticholinergics – scopolamine  
• Anxiolytics – lorazepam  
• Promethazine  
• Diuretics  
• Bronchodilators  
• Antitussives  
• Palliative sedation

Secretions

- Common in patients with pulmonary or neurologic symptoms
- High incidence in last days to hours of life:
  - Poor mucociliary clearance (couple with poor cough reflex) -> may result in sensation of choking, dyspnea
  - Lose ability to swallow
  - As air moves over the secretions in the oropharynx and bronchi a “gargling” or “rattling” sounds results

- No evidence that patients find this ‘death rattle’ disturbing, evidence from bereaved surveys suggests the noises can be disturbing to the patient’s visitors and caregivers who may fear that the patient is choking to death

- Predictor of death within 16-23 hours

Secretions – Nonpharmacological Management

- Position the patient on their side or in a semi-prone position to facilitate postural drainage
- A minute or two of Trendelenburg positioning can be used to move fluids up into the oropharynx for easier removal; aspiration risk is increased, however
- Gentle oropharyngeal suctioning is used although this can be ineffective when fluids are beyond the reach of the catheter. Frequent suctioning is disturbing to both the patient and the visitors (avoid deep suctioning)
- Reduction of fluid intake; discontinuation of IV fluids
- Communication with family and caregivers aimed to address associated fears and interpretations
- More frequent mouth care (some therapies can be extremely drying)
Secretions – Pharmacologic Management

1. **Atropine SL – 1% drops**
   - Often the drug of choice for hospice agencies (cost)
   - Use the ophthalmic drops sublingually – **2 drops SL every 2-4 hours as needed for increased secretions**
   - Crosses the into the CNS – increase risk of confusion, blurred vision, delirium, dry mouth, urinary retention
   - Generally avoid in patients delirium or altered mental status (i.e., end stage dementia)

2. **Glycopyrrolate**
   - Not effective by mouth – given IV or SQ generally – **0.2 mg every 4 hours as needed for increased secretions**
   - Quaternary amine – does not readily cross into the CNS
   - Best option for patients with delirium or concern for inducing delirium
   - Consider IV vs SQ – SQ may irritate some patients
   - Much more expensive

3. **Scopolamine**
   - Patch – can be effective “background” management of secretions – ~**1.5 mg q72h**
   - Place on hairless skin just behind the ear – more than one patch may be used at a time
   - Irritation at the side of application

Assessment Questions #1

Mr. Burns is an 68 year old male who was recently diagnosed with unresectable metastatic pancreatic cancer. His life expectancy is estimated to be hours to days. He is struggling with pain, delirium, and excessive respiratory secretions. The gargling and rattling sounds are disturbing to his family. Which of the follow secretion management options would be **best** for Mr. Burns at this time?

A. **Glycopyrrolate 0.2 mg IV every 4 hours PRN**
B. Scopolamine patch – apply 1 patch every 72 hours
C. Atropine SL drops – 2 drops every 15 minutes schedule
D. Diphenhydramine 50 mg IV every 6 hours
E. Do not treat his secretions
Delirium

- Delirium may be hyperactive/agitated, hypoactive, or mixed
- The hallmark of delirium is an **acute change in the level of arousal**
  - Supporting features include altered sleep/wake cycle, mumbling speech, disturbance of memory and attention, and perceptual disturbances with delusions and hallucinations
- Most common type is **hypoactive** – harder to diagnose / identify
  - 80% of palliative care patients
  - Can be mistaken for depression
- Terminal delirium:
  - Patient in the final days/weeks of life, where treatment of the underlying cause is impossible, impractical, or not consistent with the goals of care
  - Often difficult to reverse and may require high levels of sedation

Medication induced delirium

- **Always assume it’s caused by medications until proven otherwise. Always!**
- Most common cause of delirium in palliative patients – up to 60%
- Medications of interest:
  - Anticholinergic agents ([anti-secretion agents](https://www.palmyra.com), anti-emetics, anti-histamines, tricyclic antidepressants, SSRIs, skeletal muscle relaxants)
    - Atropine, prochlorperazine, diphenhydramine (Benadryl), amitriptyline
  - Sedative-hypnotics
    - Benzodiazepines (i.e., lorazepam), zolpidem, eszopiclone
  - Analgesics
    - Some opioids (i.e., morphine) are more anticholinergic; NSAIDS
  - Cardiac medications
    - Beta-blockers (hypo-perfusion), digitalis, antiarrhythmic drugs
  - Polypharmacy in general, drug interactions, [medication withdrawal](https://www.integratedcancerinfo.com/medication withdrew)
General MOA – drug-induced delirium

Delirium – cont’d

- Other causes of delirium:

<table>
<thead>
<tr>
<th>Infections</th>
<th>Fluid imbalance (dehydration)</th>
<th>Immobilization / restraints</th>
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<tbody>
<tr>
<td>Electrolyte disarray</td>
<td>Constipation</td>
<td>Pressure ulcers / wounds</td>
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<tr>
<td>Undertreated pain</td>
<td>Sensory deprivation</td>
<td>Bladder catheters</td>
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<tr>
<td>Alcohol withdrawal</td>
<td>Urinary retention</td>
<td>Fractures</td>
</tr>
<tr>
<td>Liver failure</td>
<td>Insomnia</td>
<td>Illicit drugs</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>Malnutrition</td>
<td>Depression</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Post-op</td>
<td>Paraneoplastic syndromes</td>
</tr>
<tr>
<td>History of stroke</td>
<td>Sudden withdrawal of meds</td>
<td>Pulmonary embolism</td>
</tr>
</tbody>
</table>
Delirium – treatment

- Prevention is key – environmental optimization
- Non-pharmacologic management - #1 treatment modality
- Fix underlying etiology of delirium – resolution in days to weeks

**Pharmacologic therapy:**

- Haloperidol 0.5 – 2mg every 1 hour as needed (PO, SL, or IV)
  - Dosing can be changed to every 6-12 once stable
  - Avoid IM if possible
- Risperidone 0.25-6 mg every 12 hours to nightly (PO)
- Olanzapine 2.5 – 20 mg once daily (PO) – ODT available
- Quetiapine 12.5-400 mg daily in 2-3 divided doses (PO)
- Melatonin 0.5 – 9 mg nightly (lower doses in older adults)

**Black box warning:**
- Increase mortality for dementia-related psychosis

- Benzodiazepines – lorazepam in refractory cases or severe agitation
  - Rare cases it’s effective
  - Beneficial if delirium is from alcohol withdrawal

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Delirium – recent evidence

- Double-blind, randomized trial in which 247 patients in inpatient hospice or a hospital palliative care service with a life-limiting illness (cancer in 88 percent), mild to moderately severe delirium
  - Randomly assigned to risperidone, haloperidol, or placebo – every 12 hours for 72 hours
  - Also received subcutaneous midazolam PRN for “severe distress”
  - Tracked the Nursing Delirium Screening Scale [NuDESC]
  - Patients in the atypical antipsychotic group reported:
    - Great delirium severity
    - Increased use of SQ midazolam
    - More extrapyramidal symptoms
    - Worse short-term survival
- How do we meaningfully interpret these data?
Assessment Questions #2

Which of the following options is a **TRUE** statement?

A. Haloperidol is never the drug of choice for the management of acute delirium because of its severe extrapyramidal side effects
B. Methylphenidate should be used in all patients with hypoactive delirium regardless of the cardiac history
C. There is no difference in efficacy between the second generation atypical antipsychotics for the treatment of delirium
D. Risperidone is the most sedating of all of the second generation atypical antipsychotics

Insomnia

- Condition of impaired sleep, with difficulties in initiating or maintaining sleep, and/or experiencing sleep as nonrestorative and unrefreshing
- Common symptom in many palliative care patients
- Lack of or poor sleep may exacerbate other symptoms (pain, anxiety, depression, cancer-related fatigue), contribute to poor quality of life, and can be predictive of developing new psychiatric disorders
- Approach and treatment to insomnia in these patients should be individualized
- Treat symptoms contributing for poor sleep (pain, chronic cough, hiccups, etc.)
- Review medications (opioids, steroids, beta-receptor agonists, many antidepressants, and psychostimulants) – all can contribute to insomnia
Insomnia

- Sleep hygiene is an important factor contributing to insomnia
- May be counseled by any health care provider (i.e., as a pharmacist I discuss how pharmacotherapy will NOT be as beneficial without optimizing sleep habits first)
- Have a regular sleep schedule at night (the body likes consistency)
- Avoid caffeine, nicotine, and spicy foods late in the day
- Avoid alcohol 4-6 hours prior to going to sleep
- Avoid or limit length of naps during the day (<1 hour prior to 3 PM)
- Use the bed for sleeping and intimacy
- Avoid exercising too close to bedtime (within 4 hours)
- Bath or shower 1-2 hour prior to bedtime
- Keep your room cool, dark, and quiet (optimal sleeping temperature is 67°F)

Insomnia - pharmacotherapy

Attempt optimizing sleep hygiene and nonpharm therapies first

- Melatonin -> 0.5 – 9 mg PO at bedtime
  - Generally well tolerated; start with lower doses in the elderly; some immunomodulatory effects (effects in solid organ and stem cell transplant?)
- Ramelteon -> 8 mg PO daily at bedtime
  - Melatonin receptor agonist; similar concerns as melatonin
- Mirtazapine -> 7.5 – 15 mg PO at bedtime
  - Great for patients with symptom clusters (appetite, anxiety, nausea, headaches, pain); with higher doses we lose some of the histamine selectivity
- Trazodone -> 25 – 100 mg PO at bedtime
  - Some anticholinergic effects – dry mouth, excessive sedation, urinary retention, caution in elderly; some “hang over” effect
- Zolpidem -> 5 – 10 mg immediate release PO at bedtime
  - Controlled release formulations are available
  - Altered PK in women and elderly patients – avoid or start with low doses
  - Increased risk of falls and other “night time disorders” – sleep eating, sleep driving
- Eszopiclone -> 1 – 3 mg PO at bedtime
  - Increased risk of falls, especially in older adults
Insomnia - pharmacotherapy

Therapies to avoid:

- **Opioids:**
  - Can paradoxically make insomnia worse
  - Proven to be ineffective and actually alter natural sleep/wake cycles

- **Antihistamines** (i.e., diphenhydramine):
  - Advil PM™, Tylenol PM™ - not effective for sleep latency, can have significant “hang over” effect
  - Anticholinergic effects increase risk of falls, urinary retention, xerostomia, constipation
  - Pharmacodynamic effects are exacerbated in older adults

- **Benzodiazepines** (temazepam, lorazepam):
  - One of the highest fall risk medications
  - May induced delirium in older adults
  - Add to existing CNS burden of medications; risk of respiratory depression with opioids

Refractory nausea and vomiting

- One of the most bothersome symptoms for patients with advanced cancer
- Many etiologies of chronic, refractory nausea and vomiting
- Understanding the underlying mechanism is important in targeting the correct receptors
- Each of our available therapies have different adverse effects profiles that need to be individualized
### Refractory N/V – drug targets

<table>
<thead>
<tr>
<th>Targets/neurotransmitters</th>
<th>Physical location</th>
<th>Type of N&amp;V</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT/5-HT3</td>
<td>Gut to NTS; EC in the gut (ROS from chemo and release of serotonin) – direct signal or sensitize vagus nerve to additional stimuli (substance P)</td>
<td>Acute</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Widely distributed in the CNS</td>
<td>Delayed</td>
</tr>
<tr>
<td>Substance P/NK-1</td>
<td>Vagus nerve to NK-1 receptors in the CTZ (central and peripheral nervous system – gut, area postrema, and NTS)</td>
<td>ALL</td>
</tr>
<tr>
<td>Others (GABA, histaminic, muscarinic, CNB)</td>
<td>Primarily CNS mediated; possibly the root causes of vestibular types of nausea and vomiting</td>
<td>ALL</td>
</tr>
</tbody>
</table>

### Refractory N/V – etiology specific

<table>
<thead>
<tr>
<th>Cause</th>
<th>Pearls</th>
</tr>
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<tbody>
<tr>
<td>Medications*</td>
<td>This includes anti-cancer therapies (chemo in particular); opioids; some anticholinergic meds; cardiac meds (digoxin); vitamins; hormones; polypharmacy in itself can be a risk factor (&gt;5 meds) – the list is endless</td>
</tr>
<tr>
<td>Radiation</td>
<td>Often accompanied by mucositis, esophagitis, and poor nutrition; higher likelihood with larger radiation field (i.e., &gt; with whole body o)</td>
</tr>
<tr>
<td>Physical tumor burden</td>
<td>Common with GI and ovarian cancers; neuroendocrine tumors secrete 5HT that can cause diarrhea and nausea; ascites</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>Hypercalcemia; hyperglycemia; hypnatremia</td>
</tr>
<tr>
<td>Acid-related</td>
<td>From medications, tumor, diet, or a combination of all of these; ethanol abuse</td>
</tr>
<tr>
<td>Constipation/obstruction</td>
<td>Common in advanced cancers; fix underlying cause (i.e., opioid-induced constipation, etc.)</td>
</tr>
<tr>
<td>Centrally mediated</td>
<td>CNS tumors – think increased ICP and vasogenic edema; ataxia; vertigo (motion sickness)</td>
</tr>
<tr>
<td>Psychomimetic</td>
<td>Anxiety, depression, insomnia</td>
</tr>
<tr>
<td>Post-operative</td>
<td>Anesthesia; common with GI cancers</td>
</tr>
<tr>
<td>Infections</td>
<td>Antimicrobial +/- actual infection (GI source vs CNS)</td>
</tr>
</tbody>
</table>

*medications typically add to nausea/vomiting even though there may be an another obvious cause (i.e., obstruction)
Refactory N/V – pharmacotherapy options

- Serotonin antagonists
- Corticosteroids
- Neurokinin-1 receptor antagonist
- Olanzapine
- Dopamine antagonists
- Benzodiazepines
- Cannabinoids
- Antihistamines/anticholinergics

Refactory N/V – pharmacotherapy

<table>
<thead>
<tr>
<th>Serotonin Antagonist</th>
<th>High Emetic Risk</th>
<th>Moderate Emetic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron (Zofran)</td>
<td>PO: 16-24 mg</td>
<td>PO: 8-24 mg</td>
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<tr>
<td></td>
<td>IV: 8-16 mg</td>
<td>IV: 8-16 mg</td>
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<tr>
<td>Granisetron (Kytril)</td>
<td>PO: 2 mg</td>
<td>PO: 1-2 mg</td>
</tr>
<tr>
<td></td>
<td>IV: 1 mg</td>
<td>IV: 1 mg</td>
</tr>
<tr>
<td></td>
<td>SQ: 10 mg</td>
<td>Transdermal patch</td>
</tr>
<tr>
<td>Dolasetron (Anzemet)</td>
<td>PO: 100 mg</td>
<td>PO: 100 mg</td>
</tr>
<tr>
<td>Palonosetron (Aloxi) +/-</td>
<td>PO: 0.5 mg</td>
<td>PO: 0.5 mg</td>
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<tr>
<td>netupitant</td>
<td>IV: 0.25 mg</td>
<td>IV: 0.25 mg</td>
</tr>
<tr>
<td>Tropisetron</td>
<td>Not available in the US</td>
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<tr>
<td>Ramosetron</td>
<td>Not available in the US</td>
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Refractory N/V – pharmacotherapy

5HT3 antagonists – pearls

- Blocks 5HT-3 receptors in GI and CNS tract
- For ACUTE nausea/vomiting; synergistic effect with steroids
- IV and PO equally as effective

- Monitoring:
  - Single IV doses >16 mg are not recommended due to QTc prolongation
  - What’s the deal with QTc prolongation and ondansetron??
  - Constipation, headache
  - Ondansetron may mask progressive ileus and/or gastric distension; monitor for decreased bowel activity.
  - Serotonin syndrome
  - Caution with mild hepatic impairment (Child-Pugh class C)

- Other products:
  - Rectal suppositories (compounded), film (Zuplenz)

Refractory N/V – pharmacotherapy

Corticosteroids

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Dexamethasone (Decadron)</td>
<td>4-8 mg BID (variable)</td>
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<td>8-12 mg daily for CINV</td>
</tr>
<tr>
<td>Methylprednisolone (Solu-Medrol)</td>
<td>40-125 mg IV</td>
</tr>
<tr>
<td>Prednisone (Deltasone)</td>
<td>Unknown for nausea</td>
</tr>
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</table>
Refractory N/V – pharmacotherapy

**Corticosteroids – pearls**

- Preferred corticosteroid (no mineralocorticoid activity) for CINV and delayed, chronic, refractory N/V
- Mechanism of action unknown (?)
- Beneficial for N/V associated with an inflammatory component – CNS mets, bowel obstruction, visceral pain (liver capsule stretch)
- Inducer of CYP3A4/CYP2C9 – think drug-drug interactions

**Monitoring:**
- Endocrine effects - Glucose, diabetes, weight gain, osteoporosis
- Mental status (acute psychoses, AMS, insomnia – confounding issues in palliative care)
- Long term use – GI ulceration; skin thinning/breakdown; immunosuppression; myopathy
- Cardiovascular (fluid retention, hypertension, clots)
- Perineal irritation – rectal burning with rapid IV push >10 mg, more common in females (resolves in minutes)
- When is a taper needed? >2 weeks of use of >20 mg pred or equivalent

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**Refractory N/V – pharmacotherapy**

**Olanzapine**

<table>
<thead>
<tr>
<th>Med</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>2.5 – 10 mg daily</td>
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<td></td>
<td>CINV - 10 mg D1 of chemo then D2-4</td>
</tr>
<tr>
<td>[Off-label]</td>
<td>Breakthrough N/V – 10 mg daily for 3 days</td>
</tr>
</tbody>
</table>

Dosing is all over the place for chronic, refractory N/V associated with advanced cancer – 5 mg twice daily, 10 mg nightly, 2.5 mg TID? (with PRN dosing in some case reports)
Refractory N/V – pharmacotherapy

Olanzapine – pearls

- Multiple receptor activity (5HT3, Dopamine, alpha 1 receptors)
- Great for symptom clusters (insomnia, anxiety, poor appetite/cachexia, neuropathic pain)
  - “Olanzapine may reduce opioid requirements and be ‘opioid sparing’ in cancer patients with uncontrolled pain who also have cognitive impairment or anxiety”
- CINV, chronic/refractory N/V, nausea associated with obstruction
- Increased risk of mortality in patients with dementia
- Fewer drug interactions than other anti-emetic therapies (hepatic)

- Monitoring:
  - Sedation, orthostatic hypotension (falls), moderate anticholinergic effects
  - Leukopenia, neutropenia, and agranulocytosis
  - Increase in cholesterol and TGs; diabetes
  - Esophageal dysmotility/aspiration

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Neurotransmitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT3, D_2, D_3, 5-HT_1, Acetylcholine, Histamine</td>
<td></td>
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</tbody>
</table>

Dopamine Antagonists

<table>
<thead>
<tr>
<th>Med</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prochlorperazine (Compazine)</td>
<td>5-10 mg 3-4 times daily; 25 mg daily (suppository)</td>
</tr>
<tr>
<td>Promethazine (Phenegran)</td>
<td>12.5-25 mg every 6 hours</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>0.5-1 mg every 6 hours as needed; much higher dosing with refractory N/V</td>
</tr>
<tr>
<td>Metoclopramide (Reglan)*</td>
<td>5 mg four times a day (30 minutes prior to meals and at bedtime)</td>
</tr>
<tr>
<td></td>
<td>CINV dosing varies</td>
</tr>
</tbody>
</table>
Refractory N/V – pharmacotherapy

Prochlorperazine – pearls

• Most beneficial for \textit{opioid induced nausea} (CTZ mediated)
• Caution in older adults due to sedating properties/anticholinergic effects
• Consider symptom clusters too – headache (w/ diphenhydramine), hiccups
• Recent shortages at UVA have limited us of IV prochlorperazine

• Monitoring:
  – Sedation, dizziness, dry mouth, drop in blood pressure, falls
  – Extrapyramidal symptoms
  – Potential to increase risk of aspiration
  – Possible accumulation in patient with moderate to severe hepatic impairment
    (n-demethylation in the liver – phase I enzymes; N-desmethyl prochlorperazine
    [major active metabolite])

Refractory N/V – pharmacotherapy

Promethazine - pearls

• Based on mechanism – better for nausea associated with vertigo and gastroenteritis due
to infections and inflammation
• Caution in older adults due to sedating properties/anticholinergic effects
• Parenteral administration – issues with chemical irritation to tissue (burning, pain,
thrombophlebitis, tissue necrosis, and gangrene); SQ contraindicated; deep IM
  preferred
• Injection is restricted to adult and pediatric Hematology/Oncology patients who have
  central line access and pharmacist-only order entry

• Monitoring:
  – Sedation, anticholinergic effects (this may also be responsible for anti-emetic
    activity [i.e., muscarinic effects]), falls
  – Route of administration
Haloperidol - pearls

- Often our **drug of choice** in palliative care for refractory, “breakthrough” N/V
- Low dose (e.g., 0.5 mg per dose) can be extremely effective for nausea and for other symptom clusters
- Look out for patients or families googling “Haldol” – explain it’s for N/V and not because their loved one is crazy
- Hepatic metabolism – glucuronidation, CYP3A4 oxidation (no established reduction in liver impairment, though)

- Monitoring:
  - QTc prolongation, particularly with IV therapy
  - Anticholinergic effects – caution with decrease GI motility, paralytic ileus (low risk)
  - EPS symptoms > olanzapine

Metoclopramide – Pearls

- Giving diphenhydramine prior may reduce EPS symptoms (recommended for CINV and scheduled dosing) – mixed clinical benefit; caution in older adults
- Dosing adjustments may be needed with CYP2D6 inhibitors
- CrCl <40 ml/min – administer 50% of normal dose (for IV)
- CrCl <60 mg – 5 mg four times daily or 10 mg twice daily (max 20 mg/day)
  - Dose adjustments with ESRD
- Rapid IV administration may be associated with a transient (but intense) feeling of anxiety and restlessness, followed by drowsiness

- Monitoring:
  - EPS symptoms
  - Cardiac – QTc prolongation
  - Prescribing inertia with metoclopramide?
Refractory N/V – pharmacotherapy

Benzodiazepines

<table>
<thead>
<tr>
<th>Med</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam* (Ativan)</td>
<td>0.5-2 mg every 6 hours</td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.5-2 mg daily</td>
</tr>
</tbody>
</table>

* Typically the benzo of choice for anticipatory N/V

Lorazepam – pearls

- No inherent anti-emetic properties – somewhat complex mechanism
  - Anxiolytic properties, sedating
- Caution in older adults – may worsen or cause delirium (especially in the hospital)
  - BUT if you’re going to use a benzodiazepine for older adults, lorazepam is the best
  - Phase II metabolism is intact vs phase I enzymes reduced in elderly
- Should NOT be used as the sole “anti-emetic” medication
- Caution with opioids – increased risk of respiratory depression
- If it for anticipatory N/V – is future therapy planned?
- SL route has adequate buccal absorption (can give with water, juice, applesauce, or pudding

- Monitoring
  - Mental status (sedation), anticholinergic properties
  - Need to taper – tolerance develops relatively quickly – my rule of thumb is if used scheduled for >5 days
  - Duration of therapy?
  - Aspiration risk – important for palliative patients at EOL
Refractory N/V – pharmacotherapy

Cannabinoids

<table>
<thead>
<tr>
<th>Med</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol (Marinol)</td>
<td>2.5-10 mg 3 to 4 times daily; studied 5 mg/m2 prior to chemo and every 2-4 hours</td>
</tr>
<tr>
<td>Nabilone (Cesamet)</td>
<td>1-2 mg twice daily; maximum 6 mg/day (in divided dosing)</td>
</tr>
</tbody>
</table>

Refractory N/V – pharmacotherapy

Dronabinol – Pearls – (CIII)

- Endogenous cannabinoid system is important in emetic response
- Cannabis sativa L. - delta-9-tetrahydrocannabinol (delta-9-THC) – synthetic
- Limited to the management of breakthrough nausea and vomiting caused by chemotherapy
- Unclear benefit with chronic, non-chemotherapy related N/V
- Studied in combination with ondansetron and prochlorperazine
- What about medical marijuana?
  - Hyperemesis syndrome
  - Immunosuppression?
- CYP2C9 genetic polymorphism - possible
- Elderly
  - Monitoring:
    - Vertigo, xerostomia, hypotension, dysphoria, depression, hallucinations
    - Increased risk of arterial hypotension (>20% drop in BP from baseline in studies)
    - New or worsening paradoxical nausea, vomiting, and/or abdominal pain may occur with synthetic cannabinoids
    - Dronabinol contains sesame oil and poses a risk of anaphylaxis to those with a hypersensitivity to sesame seeds or nuts
    - Relative contraindication in patients with seizures
Refactory N/V – pharmacotherapy

“Other” Therapies – secretions related or vertigo

<table>
<thead>
<tr>
<th>Med</th>
<th>Dosing</th>
<th>Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>1 patch every 72 hours</td>
<td>Strong anticholinergic effects; watch out for overly sedated or delirious patients</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>0.1-0.2 mg every 6 hours</td>
<td>Peripheral action only; less likely to cause adverse effects compared to other anticholinergic drugs</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>12.5-25 mg every 6 hours</td>
<td>Avoid in elderly if you can; can increase risk of delirium</td>
</tr>
<tr>
<td>Meclizine</td>
<td>25-100 mg in divided daily doses</td>
<td>Antihistamine – great for vertigo; caution in older adults</td>
</tr>
<tr>
<td>Octreotide</td>
<td>200 mcg to 900 mcg/day in 2-3 divided doses</td>
<td>N/V associated with obstructions; costly; often on shortages; first line rec in MASCC guidelines for advanced cancer N/V</td>
</tr>
</tbody>
</table>

Hiccups

- Distressing to patients and families – may diminish quality of life
- A hiccup is an involuntary reflex involving the respiratory muscles of the chest and diaphragm, mediated by the phrenic and vagus nerves and a central (brainstem) reflex center
  - Acute hiccups <48 hours
  - Persistent hiccups >48 hours
  - Intractable hiccups >1 month
- **Etiology of hiccups:**
  - Stress/excitement
  - Malignancy (high with solid tumors / head & neck cancers)
  - Esophageal or gastric distention
  - Liver disease
  - Uremia
  - Corticosteroids
  - CNS lesions
  - Chemotherapy
  - Unknown cause
Hiccups – management

**Pharmacologic therapies:**
- **Chlorpromazine** – only FDA approved therapy -> 25-50 mg PO 3-4 times daily
  - Can also be given slow IV infusion
- **Haloperidol** -> 2-5 mg PO x 1 “load” then 1-4 mg PO 3 times daily
- **Gabapentin** -> 300-400 mg PO 3 times daily (especially if chronic cough is present)
- **Baclofen** -> 5 mg PO 3 times daily
  - Studied in randomized controlled study – found to provide symptomatic relief in some patients
- **Metoclopramide** -> 10 mg PO 4 times daily
- **Nifedipine** -> 10 mg PO twice daily

**Non-pharmacologic therapies:**
- Gargling with water
- Biting a lemon
- Swallowing sugar
- Producing a fright response
- Breath holding
- Hyperventilation

https://www.mypcnow.org/blank-mkw97

Pain

- **Number one complaint of palliative care patients**
- Large impact on patient functional status and quality of life
  - Dying in pain is a fear of many patients

- **Many treatment modalities for pain:**
  - Non-pharmacologic (mindfulness based stress reduction, TENS)
  - Non-opioids (NSAIDs, acetaminophen)
  - Opioids
    - Various routes of administration:
      - PO, SL, IV, IM, SQ, intranasal, rectal, transdermal, intra-articular, epidural, intrathecal
    - Adjuvant therapies
      - Antidepressants, anticonvulsants, etc.
    - Interventional therapies (blocks, spinal cord stimulators, etc)
  - Radiation
  - “Root cause” analgesics
### Pain - continued

#### Drug Brand Names®

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Names®</th>
<th>Drug</th>
<th>Brand Names®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>MS Contin; Kadian; Arymo ER; Duramorph</td>
<td>Codeine</td>
<td>n/a</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Dilaudid; Exalgo</td>
<td>Tramadol</td>
<td>Ultram; ConZip; Enova-RX; Synapryn; FusePaq</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Hysingla ER; Zydro ER; combination products</td>
<td>Tapentadol</td>
<td>Nucyta; Nucyta ER</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>OxyContin; Roxicodone; Xtampza ER; Oxaydo</td>
<td>Ketamine</td>
<td>Ketalar</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Opana; Opana ER</td>
<td>Meperidine</td>
<td>Demerol</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Duragesic; Sublimaze; Abstral; Actiq; Fentora; Ionsys; Lazanada; Subsys</td>
<td>Buprenorphine*</td>
<td>Belbuca; Buprenex; Butrans; Probuphine Implant Kit</td>
</tr>
<tr>
<td>Methadone</td>
<td>Dolophine; Methadone HCl intensol; Methadose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Opioid Dose Frequency

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (PO)</td>
<td>15-30 mg</td>
<td>Every 3-4 hours</td>
</tr>
<tr>
<td>Morphine (IV)</td>
<td>2.5-5 mg</td>
<td>Every 3-4 hours</td>
</tr>
<tr>
<td>Hydromorphone (PO)</td>
<td>2-4 mg</td>
<td>Every 3-4 hours</td>
</tr>
<tr>
<td>Hydromorphone (IV)</td>
<td>0.2-1 mg</td>
<td>Every 3-4 hours</td>
</tr>
<tr>
<td>Oxycodone (PO)</td>
<td>5-10 mg</td>
<td>Every 3-4 hours</td>
</tr>
<tr>
<td>Oxymorphone (PO)</td>
<td>5-10 mg</td>
<td>Every 4-6 hours</td>
</tr>
<tr>
<td>Tramadol (PO)</td>
<td>50-100 mg</td>
<td>Every 4-6 hours</td>
</tr>
<tr>
<td>Tapentadol (PO)</td>
<td>50-100 mg</td>
<td>Every 4-6 hours</td>
</tr>
</tbody>
</table>
## Pain - continued

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Time to effect</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (oral)</td>
<td>30-40 mins</td>
<td>3-5 hours</td>
</tr>
<tr>
<td>Morphine (IV)</td>
<td>5-10 mins</td>
<td>~3 hours</td>
</tr>
<tr>
<td>Codeine (oral)</td>
<td>40-60 mins</td>
<td>4 hours</td>
</tr>
<tr>
<td>Hydrocodone (oral)</td>
<td>20 mins</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Oxycodone (oral)</td>
<td>10-15 mins (peak 60 mins)</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Hydromorphone (oral)</td>
<td>15-30 mins</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Hydromorphone (IV)</td>
<td>5 mins</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Fentanyl (patch)</td>
<td>6-12 hours</td>
<td>72 hours</td>
</tr>
<tr>
<td>Fentanyl (IV)</td>
<td>Seconds to minutes</td>
<td>30 mins – 2 hours</td>
</tr>
<tr>
<td>Tramadol (oral)</td>
<td>60 mins</td>
<td>6-8 hours</td>
</tr>
<tr>
<td>Methadone (oral)</td>
<td>30-60 mins</td>
<td>Variable – 6-8 hours</td>
</tr>
</tbody>
</table>

### True or False

Tramadol is not an opioid.

**False**

Tramadol is a weak agonist to the mu-opioid receptor. It also works by blocking re-uptake of norepinephrine and serotonin. Inappropriate use of tramadol (elderly patient with renal dysfunction) can lead to sedation, falls, confusion, or even respiratory depression.
Assessment Questions #4

TRUE OR FALSE

Opioid-induced constipation gets better over time (i.e., tolerance develops).

FALSE

Tolerance to constipation never develops while on opioid therapy. A bowel regimen is a vital part of chronic opioid management.

Assessment Questions #5

TRUE OR FALSE

Methadone is only used for opioid maintenance therapy

FALSE

Methadone is a fantastic analgesic therapy that can be used when escalating doses of other opioids are ineffective or result in intolerable side effects. Methadone is great for cancer pain but does have complicated pharmacokinetics and pharmacodynamics. Obtain pain or palliative consultation when considering methadone therapy.
Tramadol O’ Tramadol

- Tramadol is an analgesic that has some activity at mu receptors
- It also inhibits the reuptake of serotonin and norepinephrine
- A systematic review found that tramadol improved functional outcomes and pain in patients with fibromyalgia
- Tramadol versus NSAIDs versus nortriptyline for chronic pain – no benefit of tramadol

- **Drawbacks of tramadol:**
  - Lower seizure threshold – first thing you should do when you prescribe tramadol is to check if they have a seizure history (even if they are on it at home)
  - Tramadol is often poorly tolerated (GI upset)
  - Pharmacogenomic differences – potent active metabolite – O-desmethyltramadol
  - Tramadol can increase the risk of serotonin syndrome – though rare
  - Induced severe hypoglycemia

- Small place in therapy for young cancer patients with mixed typed pain

People who should not be started on tramadol:
1. 91-year-old women
2. all other people

91 yo F with tramadol induced hyponatraemia -> fall -> Colles' # of dominant wrist. Medications matter in the elderly pt (https://twitter.com)
Methadone (for analgesia)

- Most data for cancer-related pain
- Racemic mixture of R and S isomers
- NMDA antagonist (both, mostly S)
- Mu, kappa, delta-opioid receptor agonist (R-methadone)
- Strong inhibitor of serotonin and NE reuptake (S-methadone)
- Potassium channel blocker (Human-Ether-a-Go-Go receptor, S)
- Possible activity on acetylcholine/muscarinic receptors

- Mechanism is so important because of the following:
  - Less traditional opioid adverse effects
  - More in depth understanding of adverse effect profile
  - Less tolerance due to mixed activity
  - Broader application in regards to type of pain treated (i.e., better analgesia, neuropathic pain)

Methadone mental checklist

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication (pain or maintenance therapy)</td>
<td>☐</td>
</tr>
<tr>
<td>Is the patient elderly or extremely cachectic</td>
<td>☐</td>
</tr>
<tr>
<td>For new starts, what is the patient's current OMEs?</td>
<td>☐</td>
</tr>
<tr>
<td>Does the patient have adequate PRN or breakthrough therapy?</td>
<td>☐</td>
</tr>
<tr>
<td>Is this a doses change?</td>
<td>☐</td>
</tr>
<tr>
<td>Dose Conversions:</td>
<td></td>
</tr>
<tr>
<td>Other long acting opioids prescribed?</td>
<td>☐</td>
</tr>
<tr>
<td>Recent QTc measurement</td>
<td></td>
</tr>
<tr>
<td>Drug-drug interactions reviewed?</td>
<td>☐</td>
</tr>
<tr>
<td>Does the patient have liver impairment?</td>
<td>☐</td>
</tr>
<tr>
<td>Is the patient also taking a benzodiazepine?</td>
<td>☐</td>
</tr>
<tr>
<td>Is a bowel regimen ordered?</td>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Morphine (OME)</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg</td>
<td>20-30%</td>
</tr>
<tr>
<td>100-300 mg</td>
<td>10-20%</td>
</tr>
<tr>
<td>301-600 mg</td>
<td>8-12%</td>
</tr>
<tr>
<td>601-1000 mg</td>
<td>5-10%</td>
</tr>
<tr>
<td>&gt;1000 mg</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

There is not a linear relationship when converting to methadone from oral morphine. The higher the daily morphine equivalent dose the more potent methadone is, and conversion to methadone is more of a process than a calculation. In general, the starting methadone dose should not exceed 30 to 40 mg/day, even in patients on high doses of other opioids.
### Adverse effects

#### Pain – opioid adverse effects

<table>
<thead>
<tr>
<th>First</th>
<th>Second</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation*</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Sedation</td>
<td>Tremor</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Pruritus/rash</td>
</tr>
<tr>
<td>Short term cognitive impairment</td>
<td>Rebound headaches</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Delirium</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>Edema</td>
</tr>
<tr>
<td>Sweating</td>
<td>Bloating</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>Reflux</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Tachycardia</td>
</tr>
</tbody>
</table>

#### Uncommon adverse drug effects

- Hyperalgesia
- Adrenal insufficiency
- Low testosterone
- Increase intracranial pressure
- Long term cognitive dysfunction
- Dystonic reactions

*Tolerance does NOT develop*
### ADEs Practical Considerations

<table>
<thead>
<tr>
<th>ADE</th>
<th>Constipation</th>
<th>Sedation</th>
<th>Respiratory depression</th>
<th>Nausea &amp; Vomiting</th>
<th>Pruritus</th>
<th>Urinary retention</th>
<th>Neuroexcitation</th>
<th>Other effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation is the only opioid adverse effect in which tolerance does NOT develop; it is the most common reason why patients discontinue opioid therapies; bowel regimen should be prescribed/ordered for all patients taking opioids; data does not support docusate use for opioid induced constipation; xerostomia and polyethylene glycol should be optimized; refractory cases consider opioid antagonist agent (e.g., naloxone/methylnaltrexone); opioid rotation is often effective in refractory cases as well.</td>
<td>Sedation is thought to be mediated by anticholinergic properties of opioids; tolerance develops over time but may reappear upon dose escalation or dosing frequency changes; therapy options include dose reduction, opioid rotation, and a trial of psychostimulants (e.g., methylphenidate 5-10 mg every morning); certain pharmacotherapy options have limited data which include amantadine, donepezil, modafinil, and dextromethorphan; nonpharmacologic therapies, such as moderate exercise, have proven effective.</td>
<td>Respiratory depression is a potential adverse effect of all opioids; sedation occurs prior to respiratory depression; monitoring vital signs, pulse oximetry, and end tidal CO2 volume can help assess current respiratory status; naloxone therapy should be provided in the setting of respiratory depression until breathing returns; combining opioids and benzodiazepines increases the risk for respiratory depression.</td>
<td>Nausea and vomiting from opioids should NOT be considered a drug allergy; morphine and codeine may cause more nausea compared to other opioids; tolerance to nausea and vomiting typically develops within 3-7 days; options for management include dose reduction, opioid rotation, anti-emetics (e.g., prochlorperazine, most effective for opioid induced nausea), and nonpharmacologic approaches.</td>
<td>Pruritus is a common adverse effect at the end of life that may be confounded or worsened by opioid administration; mediators of opioid-induced pruritus include histamine, serotonin, prostaglandins, and/or bradykinins; rule out other causes of pruritus (e.g., renal failure, other medications, allergies); management includes topical moisturizers for local itching, oral antihistamines, topical steroids, antihistamines (e.g., mirtazapine), and opioid antagonists; small studies report the use of 5HT-3 antagonists or neuromodulator antagonists for refractory pruritus; caution with first generation antihistamines in older adults and young children – potential for exaggerated adverse effects or paradoxical reactions (e.g., acute agitation).</td>
<td>Urinary retention can be painful, impair quality of life, and impact kidney function; urinary effects from opioids are mediated via mu agonist effects and typically occur in about 25% of patients; epidural administration of opioids may result in a higher incidence of urinary retention; it is important to rule out other drug induced causes (e.g., anticholinergic therapies [diphenhydramine, antipsychotics], SSRIs, benzodiazepines, NSAIDs, and calcium channel blockers); treatment modalities include short and long term catheterization, dehydrating, dose reduction, and pharmacotherapy (e.g., tamsulosin); data from case reports support use of methylnaltrexone in refractory cases.</td>
<td>Miosis is the most described neuroexcitatory effect of opioids; miosis presents as jerking or twitching of muscle groups, typically in the extremities; with escalating or repeated dosing, miosis may worsen and be followed by hyperalgesia, delirium, hallucinations, or seizures; an appropriate review of opioid history, hydration status, other exacerbating medications (e.g., haloperidol); and physical observation of miosis are essential prior to treatment; management includes dose reduction, opioid rotation, opioid sparing techniques with adjuvant therapies, or low dose benzodiazepines (other less characterized pharmacotherapy options include baclofen, gabapentin, and nifedipine).</td>
<td>Other less characterized opioid adverse effects include: hyperalgesia, sleep disturbances, cognitive impairment, hypotension/vasodilation, QTc prolongation (e.g., methadone), increased intracranial pressure, opioid endocrinopathy, immunosuppression, hearing loss, and depression.</td>
<td></td>
</tr>
</tbody>
</table>

---

### Andy’s Top 10 opioid rules

1. Always order a bowel regimen
2. Double check that you ordered a bowel regimen
3. Determine if the patient is opioid naïve or opioid tolerant
4. Check the dose (is it appropriate based the current clinical situation?)
5. Ensure the dosing interval makes sense based on the duration of effect of the drug and organ function
6. Screen all patients for risk of opioid abuse
7. Counsel on appropriate storage of opioids (lock boxes)
8. If opioids are discontinued, taper slowly.
9. Do not use opioids for headaches or insomnia
10. Use nonpharmacological options and non-opioid therapies if possible
### Non-opioids

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical Dosing Range</th>
<th>Max Daily Doses</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>PO: 400-800 mg every 6-8 hours PRN</td>
<td>3200 mg</td>
<td>Negative GI, cardiac, and renal effects may be seen*; increased risk of bleeding; caution in older adults; analgesic effect limited by dose ceiling; naproxen has the lowest risk of cardiac effects [1]</td>
</tr>
<tr>
<td>Naproxen</td>
<td>PO: 500 mg every 8-12 hours PRN</td>
<td>1500 mg</td>
<td></td>
</tr>
<tr>
<td>Ketorolac</td>
<td>IM: 60 mg x 1 or 30 mg every 6 hours PRN</td>
<td>IV:IM: 120 mg PO: 40 mg</td>
<td>Available as IV therapy; indicated for the short-term (up to 5 days); contraindicated for intrathecal or epidural administration due to its alcohol content; effective adjunct to opioids for painful bony metastasis [2]; not indicated for pediatric patients</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>IV: 30 mg x1 or 15-30 mg every 6 hours PRN</td>
<td>PO: 20 mg, then 10 mg every 4-6 hours PRN</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>PO: 50 mg every 8 hours PRN IV: 37.5 mg every 6 hours PRN</td>
<td>150 mg</td>
<td>Proven opioid sparing effects in cancer patients [3]; COX-2 selectivity; no data to support use of topical diclofenac for pain management in cancer patients</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>PO: 400 mg once on day one followed by 200 mg twice daily PRN</td>
<td>400 mg</td>
<td>Monitor for cardiac adverse effects; COX-2 selective inhibitor; dose adjustment required for poor metabolizers of CYP2C9*3/*3; contains a sulfonamide moiety - mixed data regarding use in patients with a &quot;sulf&quot; allergy</td>
</tr>
</tbody>
</table>

### NSAID Checklist

- Does the patient have existing or potential renal impairment? If so, is oral or IV hydration appropriate?
- Is the patient on other therapies that may harm the kidneys?
- Does the patient have risk factors for bleeding (e.g., recent GI bleed, prolonged NSAID use, elderly)?
- Is the patient on other therapies that may increase bleeding risk (e.g., fish oil)?
- Does the patient have existing cardiac disease that could be exacerbated by NSAID use?
- Should stress ulcer prophylaxis be considered?*
- Is the patient taking any over-the-counter combination products that contain an NSAID?
- Is the type of pain being treated likely to respond to an NSAID?
- If an infant or pediatric patient, is the concentration of the product appropriate for the patient’s age?
### Non-opioids

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical Dosing Range</th>
<th>Max Daily Doses</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>PO, PR: 650 mg every 4 to 6 hours PRN</td>
<td>PO: Adults: 4000 mg</td>
<td>Acetaminophen has been associated with acute liver failure; caution with OTC products containing acetaminophen - potential for duplicate therapies; IV therapy has similar analgesic activity but is more expensive; reduced dosing should also be considered for malnourished patients or with significant dehydration</td>
</tr>
<tr>
<td></td>
<td>IV: ≥50 kg: 650 mg every 4 hours or 1,000 mg every 6 hours PRN</td>
<td>Geriatric: 3000 mg Cirrhosis: 2000 mg IV: ≥50 kg: 4 g/day</td>
<td></td>
</tr>
</tbody>
</table>

**Acetaminophen Checklist**

- Does the patient have baseline liver impairment?
- Is the patient taking other drug therapies that may impact the liver (i.e., imatinib)?
- Is the patient taking other drug therapies that may interact adversely with acetaminophen (i.e., phenobarbital)?
- Based on patient characteristics, should the maximum total dose be modified?
- Is the patient taking other therapies (including combination analgesics) containing acetaminophen?
- Has the patient been counseled about avoid combination agents (e.g., prescription, OTC) containing acetaminophen?
- Has the patient been counseled about limiting alcohol consumption when utilizing acetaminophen as an analgesic?

### Adjuvant therapies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical Dosing Range*</th>
<th>Max Daily Doses</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>PO: 10-25 mg every 6-8 hours</td>
<td>Not defined</td>
<td>N-methyl-D-aspartate/glutamate receptor (NMDA) antagonist; subanesthetic doses may be effective for pain-resistant pain, neuropathic pain, hyperalgesia, and allodynia; can be given IV, SQ, PO, intranasally, rectally, and topically; paucity of large, controlled studies looking at ketamine for cancer pain, though large number of observations studies supporting use; oral ketamine solution has been effectively used for pain associated with mucositis; potential for neuropsychiatric, urinary tract, and hepatobiliary toxicity</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>PO/IV: 1-8 mg daily in the morning</td>
<td>As tolerated</td>
<td>Effective for pain from inflammation (i.e., spinal, CNS, bone metastases, capsular expansion); monitor glucose, GI intolerance, mental status changes, fluid retention; consider tapering if therapy is &gt;2 weeks; consider stress ulcer prophylaxis if pill burden is not an issue</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>IV: 4 mg every 3-4 weeks</td>
<td>4 mg</td>
<td>Best data to support analgesic benefit in multiple myeloma and breast cancer patients with bone metastases; adjustments for renal impairment required; monitor calcium levels and consider calcium/vitamin D supplementation; screen for dental issues prior to treatment to reduce risk of ONJ</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>SQ/IM: 4 units/kg every 12 hours</td>
<td>Not defined</td>
<td>Calcitonin has limited data to support short term therapy for the management of compression fractures and metastatic bone pain; consider kind of therapy if other treatment modalities are ineffective; monitor for hypercalcemia, hypersensitivity reactions, rhinitis, and epistaxis</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>PO: 300 mg every evening</td>
<td>3600 mg</td>
<td>Effective for neuropathic pain associated with malignancies and due to chemotherapies; adverse effects include dizziness, somnolence, and peripheral edema; requires dose adjustment with renal impairment; no significant drug-drug interactions exists with CYP450 system; tapering is required if on therapy for &gt;2 weeks; consider use if pain with other therapies response to gabapentin (hiccups, hot flashes, chronic cough, etc.)</td>
</tr>
</tbody>
</table>
### Adjuvant therapies – cont’d

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosage</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregabalin</strong> PO</td>
<td>150 mg daily in 2-3 divided doses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>600 mg</td>
<td>In a study comparing pregabalin, gabapentin, and placebo in cancer-related pain, pregabalin was found to be more effective in pain relief than placebo. Adverse effects include dizziness, somnolence, dry mouth, and weight gain; adjustment in renal impairment required; more expensive than pregabalin; controlled substance</td>
</tr>
<tr>
<td><strong>Duloxetine</strong> PO</td>
<td>30-60 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>120 mg</td>
<td>Serotonin-norepinephrine reuptake inhibitor (SNRI); best data supporting treatment of chemotherapy-induced peripheral neuropathy (CIPN) (i.e., oxaliplatin-induced); analgesic effects typically seen after 1 week with maximum benefit after 4 weeks; 60 mg twice daily may lead to increased efficacy but additional adverse effects evident (nausea, diarrhea, insomnia, sweating)</td>
</tr>
<tr>
<td><strong>Venlafaxine</strong> PO</td>
<td>37.5-75 mg daily (IR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>225 mg</td>
<td>Some data support use of venlafaxine one-hour prior to chemotherapy infusions for prevention of CIPN; adverse effects include sedation, headache, dizziness, and transient rise in blood pressure</td>
</tr>
<tr>
<td><strong>Amitriptyline</strong> PO</td>
<td>25-50 mg daily at bedtime</td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg</td>
<td>Therapy trial considered for younger patients with severe neuropathic pain, concomitant insomnia, or other existing nerve conditions; avoid in older adults if possible due to anticholinergic effects (e.g., dry mouth, excessive sedation, falls, orthostatic hypotension, urinary retention, constipation); tricyclic antidepressants may cause bone marrow suppression; use caution in patients with pre-existing cardiovascular disease; nortriptyline may have less anticholinergic effects; addition of gabapentin may work synergistically towards analgesia</td>
</tr>
<tr>
<td><strong>Nortriptyline</strong> PO</td>
<td>10-25 mg daily at bedtime</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>Data supporting use in neuropathic cancer pain is minimal; adverse effects include leukocytosis, thrombocytopenia, dizziness, drowsiness, ataxia, and blurred vision; rare effects include agranulocytosis, aplastic anemia, and Stevens-Johnson syndrome; monitor for drug-drug interactions</td>
</tr>
<tr>
<td><strong>Carbamazepine</strong> PO</td>
<td>100-200 mg twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1200 mg</td>
<td>Data supporting use in neuropathic cancer pain is minimal; adverse effects include leukocytosis, thrombocytopenia, dizziness, drowsiness, ataxia, and blurred vision; rare effects include agranulocytosis, aplastic anemia, and Stevens-Johnson syndrome; monitor for drug-drug interactions</td>
</tr>
<tr>
<td><strong>Lidocaine</strong> Topically</td>
<td>5% patch apply 12 hours on and 12 hours off</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 patches/single application</td>
<td>Lidocaine patches may be effective for localized pain with a neuropathic or mixed pain component; local irritation may occur at site of application; patches are relatively expensive; lidocaine infusions may be a helpful adjunctive therapy for refractory neuropathic pain or post-operatively for cancer-related surgeries (i.e., mastectomy, colorectal surgery); adverse effects include dizziness, headache, perioral tingling, and metallic taste; IV therapy also poses an increased risk of cardiac toxicity, seizures, and musculoskeletal effects</td>
</tr>
<tr>
<td><strong>Dronabinol</strong> PO</td>
<td>Not well established</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PO: 2.5 mg-10 mg 2-3 times daily</td>
<td>Not defined</td>
</tr>
</tbody>
</table>

**Adjuvant Therapy Checklist**

- Does the patient have other symptom clusters in which a specific adjuvant therapy would be effective for in addition to pain (e.g., gabapentin for neuropathic pain as well as refractory cough)?
- What is the adverse effect profile for the particular adjuvant agent?
- Does the dose need to be adjusted for hepatic or renal impairment?
- Does the therapy require therapeutic drug monitoring?
- Have drug-drug interactions been reviewed?
- Is the therapy appropriate based on the patient’s age (i.e., avoid TCA’s in elderly patients [≥65 years])
Equianalgesic dosing – lightning speed

- Don’t memorize - use your dosing equivalence charts
  - Online tools – Global rph, med calc

- Reasons for opioid rotation:
  - Drug cost and patient preference
  - Adverse effects to existing therapy (refractory constipation, hyperalgesia)
  - Development of tolerance and loss of analgesia

- Cross tolerance should be considered for EVERY patient when switching to another opioid
  - Rules of thumb for cross tolerance:
    1. If patient’s pain is under control consider 25-50% reduction in dose when converting
    2. IF patient’s pain in NOT under control consider 20% reduction or no reduction (discuss with pharmacy or palliative care in these situations)

- Methadone equianalgesic dosing is difficult – consult palliative care (>10 ways in the literature to convert dosing from oral morphine equivalents to methadone)

- Other medications with “dirty pharmacology” – tramadol, tapendatol – principles of equianalgesic dosing is more difficult

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**OPIOID CONVERSION GUIDELINES**

<table>
<thead>
<tr>
<th>0.2 mg IV HYDROmorphine</th>
<th>~ 10 mcg IV fentaNYL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 mg IV HYDROmorphine</td>
<td>~ 1 mg IV morphine</td>
</tr>
<tr>
<td>0.2 mg IV HYDROmorphine</td>
<td>~ 1 mg PO HYDROmorphine</td>
</tr>
<tr>
<td>1 mg IV morphine</td>
<td>~ 3 mg PO morphine</td>
</tr>
<tr>
<td>5 mg PO oxyCODONE</td>
<td>~ 2 mg PO HYDROmorphine</td>
</tr>
<tr>
<td>10 mg PO oxyCODONE</td>
<td>~ 15 mg PO morphine</td>
</tr>
<tr>
<td>5 mg PO oxyCODONE</td>
<td>~ 7.5 mg PO HYDROcodone</td>
</tr>
<tr>
<td>5 mg PO HYDROcodone</td>
<td>~50 mg PO traMADol</td>
</tr>
</tbody>
</table>

25 mcg/hr Transdermal fentaNYL ~ 100-140 mg PO morphine/day

*Reduce by 20-25% and titrate to effect. For methadone, buprenorphine, and fentanyl patch conversions: Contact Palliative care, Pharmacy, or Acute Pain Service 06/2018
1. Withdrawal of Life-Sustaining Therapies
2. Comfort Care Maintenance
3. Hospice Discharge (for outpatient prescriptions)

NEW guidelines at UVA

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### UVA Order Sets

#### Withdrawal of Life-Sustaining Therapies

<table>
<thead>
<tr>
<th>Order Set</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediations</td>
<td></td>
</tr>
</tbody>
</table>
- Fentanyl/Diazepam (DIALDACH) injection
  - 2 mg, intravenous, every 15 minutes, starting 10/10/18 for 4 doses, for labored breathing or pain prior to and after withdrawal of life-sustaining therapies, if symptoms appear unrelied after 4 doses, please page LPI
- morphine injection
  - 2 mg, intravenous, every 15 minutes, starting 10/10/18 for 4 doses, for labored breathing or pain prior to and after withdrawal of life-sustaining therapies, if symptoms appear unrelied after 4 doses, please page LPI

- Anxiety/Agitation
  - midazolam (Versed) injection
    - 2 mg, intravenous, every 15 minutes, starting 10/10/18 for 4 doses, for anxiety/agitation prior to and after withdrawal of life-sustaining therapies, if symptoms appear unrelied after 4 doses, please page LPI
- lorazepam (Ativan) 2 mg, intravenous

- Secretion Management
  - atropine 1% ophthalmic solution
    - 1 drop, subconjunctival, every 4 hours PPI, for increased secretions

- Additional SmartSet Orders
  - Tramadol (UPEC)

You can search for an order by typing in the header of this section.
Comfort Care Maintenance

- End of Life Guidelines

**Medications**

**Pain/Dyspnea**

Note that morphine is the preferred agent except in situations of renal insufficiency, and for concentrated oral solution is the preferred agent.

- Morphine concentrated oral solution
  - 1 mg/mL, 30 mL vial, for oral administration
- HYDROcodone concentrated oral solution
  - 5 mg/mL, 30 mL vial, for oral administration

**Nausea**

The concentrated oral solution is the preferred agent.

- LORazepam (ATIVAN) 0.5 mg/mL, 30 mL vial, for oral administration
- Dexamethasone (DEXAMETHASONE) injection
  - 1 mg/mL, 30 mL vial, for intramuscular use

**Agitation**

- Haloperidol (HALDOL) 2 mg/mL, solution
  - 30 mL vial, for intravenous injection

**Secretion Management**

- ASetransmethcine (DANSUCIN) 30 mg/mL, solution
  - 30 mL vial, for intravenous injection

**Constipation**

- Diphenoxylate (LORCET) 5 mg/5 mL tablet
  - 30 tablet, 8-12 hourly

**Hospice Discharge**

(for outpatient prescriptions)

**Discharge Medications**

- **Pain/Dyspnea**
  - Note on discharge prescription: “This is a hospice patient”
- Morphine (CONCENTRATED) 10 mg/mL, 30 mL vial
- HYDROcodone (CONCENTRATED) 1 mg/mL, 30 mL vial
- Sodium chloride 0.9% (PCA)

- **Anxiety**
  - LORazepam (ATIVAN) 2 mg/mL, concentrated solution
  - 30 mL vial

- **Agitation**
  - Haloperidol (HALDOL) 2 mg/mL, solution
  - 30 mL vial

- **Secretion Management**
  - Hospice preferred: atropine 1 % ophthalmic solution
  - Scopolamine (TRANSISER S): 1 mg/30 ML

- **Constipation**
  - Adjust dose based on patient need for regular bowel movements
  - LORCET 5 mg/5 mL tablet
  - 30 tablet, 8-12 hourly
  - Polyethylene glycol (COLONIAL) powder
    - 10 g, 3 times daily
    - 305 g, 3 times daily
Polypharmacy and deprescribing at EOL

• Polypharmacy - ≥5 medication used on a daily basis
  • Over 20 definitions in the literature

• Potentially inappropriate medications – medication that has the potential to cause an adverse drug effect or other unwanted effect:
  • Beers Criteria
  • START / STOPP criteria
  • Medication Appropriateness Index (MAI)

• Prescribing inertia

• Prescribing cascade

• Deprescribing
  • Systematic process of discontinuing medications used for the management of chronic illness as patients’ survival time decreases

Prescribing cascade

A breast cancer patient receiving doxorubicin and cyclophosphamide develops severe nausea and vomiting. She is prescribed ondansetron 4 mg every 8 hours as needed for nausea. The patient then develops a headache and mild constipation.

At her next clinic visit her labs show low magnesium and low calcium. She is given a prescription for calcium 400 mg daily and magnesium 400 mg twice daily.

She then develops stomach upset and a mild ulcer from ibuprofen. To treat her stomach upset she is given omeprazole 40 mg daily.

The patient is given ibuprofen 600 mg every 8 hours for her headache and Miralax 17 g daily for her constipation.
Polypharmacy and deprescribing at EOL

Deprescribing impact:

- Research has suggested the use of preventive medications such as aspirin, anti-hypertensives, and statins ranges between 29-51% in patients with a limited life expectancy, even though the time-frame of likely benefit for these medications may be far longer than a patient’s expected survival
- Pill-burden can lead to unnecessary adverse drug reactions and cost at the end of life

Holmes Framework:
1. Remaining life expectancy
2. Time until benefit of drug therapies
3. Individual goals of care
4. Target of the treatment (e.g., preventative versus palliative)

Deprescribing Process
1. Utilize a pharmacist if available to perform a complete medication reconciliation with focus on the respective indications
2. Consider the patient’s goals, prognosis, and risk of drug-induced harm. Additional risk factors for drug induced harm include the patient’s age and total number of medications.
3. Assess each medication’s risk/benefit ratio, with attention to treatment target and time-until-benefit.
4. Discontinue medication(s) based on priority.
5. Monitor for potential adverse drug withdrawal events.

https://www.mypcnow.org/copy-of-fast-fact-320

Questions?