Pharmacologic Pearls for End-of-Life Treatment

Traci M. White, PharmD, PhC
Pharmacist Clinician, Mesilla Valley Hospice
Assistant Professor, UNM College of Pharmacy

Disclosure
I have no actual or potential conflicts of interest to report.

Learning Objectives
- Identify commonly prescribed medications that may be appropriate for discontinuation
- List common symptoms and medications used for treating these symptoms experienced at the end-of-life
- Describe appropriate principles of pain assessment and development of a treatment plan
- Discuss medication-related adverse effects and methods of managing these problems
- Discuss alternative routes of administration and considerations for each
Patient Case

Olive Oyl is a 60 yo female admitted to home hospice with a primary diagnosis of metastatic breast cancer (mets to liver, lung and bone). Other comorbidities include HTN, hypothyroidism, CAD, atrial fibrillation and iron-deficiency anemia.

She is taking the following medications:

- Hydrochlorothiazide 25mg PO once daily
- Lisinopril 20mg PO once daily
- Metoprolol 50 mg PO twice daily
- Levothyroxine 75mcg PO once daily
- Iron sulfate 325mg PO BID
- Simvastatin 40mg PO at bedtime
- Risedronate 35mg PO once weekly
- Warfarin 2.5 mg PO daily on MWF, 5 mg PO on T/Th/Sat/Sun

Medication Review

- What is the indication?
- Is this in line with my patient’s goals?
- Is there any data to support use of this medication is the disease state/age group/comorbidities?
- Do the benefits of the medication(s) outweigh the possible risks?
- Can the patient use the medication(s) appropriately and are the directions practical?
- Is there a formulary alternative or superior medication?

Stopping Medications – “Deprescribing”

- Consider risks/benefits of each med
- Proceed with caution in stopping maintenance meds
  - Could have no effect
  - Could lead to withdrawal events/symptoms
    - Physical dependence
    - Physiologic dependence on exogenous drug (steroids)
    - Signs/symptoms of chronic disease may re-appear
Potential Barriers to Discontinuing Medications

- “My doctor said I should be on that for the rest of my life.”
- “That medication is the only reason my mom can still communicate with me.”
- “Do you want me to die of a stroke?”
- “He improved so much with that medication was started.”

Balancing Act

- Interventions for prevention of possible long-term complications
- Lack of evidence of benefit at EOL
- Risk of adverse events may outweigh benefit
- Decrease pill burden
- Decrease costs

Narrow Therapeutic Index

- Warfarin
- Digoxin
- Carbamazepine
- Phenytoin
- Theophylline
- Lithium

*List is not all-inclusive
Medication Classes to Assess for Discontinuation

- Statins
- Anticoagulants
- Antihypertensives – beta blockers, ACE inhibitors, ARBs, calcium channel blockers, diuretics
- Dementia medications
- Hypoglycemics
- Inhalers

Patient Case

- What medications could be discontinued in Mrs. Oyl’s case?
- What are the risks/benefits of each?
- How do you have these conversations with her and her family?

Symptom Prevalence in Cancer

Systematic review of most common symptoms in end stage cancer in last 7-14 days of life

- Fatigue – 88%
- Pain – 88%
- Weight loss – 86%
- Weakness – 70%
- Appetite loss – 56%
- Dyspnea – 39%
- Dry mouth – 34%
- Nervousness/anxiety – 30%
- Constipation – 29%
- Depressed mood – 19%

Teunissen, W et al. JPSM 2007:1:94-104
Commonly Used Medications

- Analgesics (opioids and non-opioids)
- Benzodiazepines
- Corticosteroids
- Anticholinergics
- Antipsychotics
- Laxatives
- Antidepressants

Individualized Approach

- Anticipate symptoms based on disease state(s)
  - Use of standard assessments
  - Frequent evaluation and re-evaluation
- Utilize a medication that treats multiple symptoms to reduce polypharmacy
- Discontinue medications that no longer contribute to symptom management
- Anticipate and treat side effects

Pain Management

- Complete the pain assessment
- Match the appropriate drug to the pain type
- Consider potential risks and side effects
- Assess the safest route of delivery
- Consider who will administer the meds and in what setting
- Determine whether the patient can find and afford the medication
- Assess the cultural, spiritual, and social context for the pain
Pain Assessment

- **P** = Provokes or palliates
- **Q** = Quality
- **R** = Region and radiation
- **S** = Severity
- **T** = Time

- Utilize appropriate, consistent pain scale

Indices of Therapeutic Effect

- **SUBJECTIVE**
  - Pain ratings
  - Description of improved functional status
    - Sleeping better
    - Performing ADLs better
    - Other

- **OBJECTIVE**
  - Number of breakthrough doses required
  - Assessment of improved functional status
    - Longer sleep
    - Able to walk further
    - Able to perform activities longer

Indices of Adverse Effects

- **SUBJECTIVE**
  - Constipation
  - Nausea
  - Sedation
  - Dizziness
  - Confusion
  - Itching
  - Problems with urination

- **OBJECTIVE**
  - Bowel movement frequency
  - # of episodes of emesis
  - Vital signs (BP, RR, HR)
  - Pupil size
  - Mini mental status exam
Dose Adjustments

- Educate for good record keeping of PRN doses
- “How many tablets per day do you need to stay comfortable?”
- Make the dosage increases count!
  - Increase the total daily dose of opioid by 25-50% for mild to moderate pain
  - Increase the total daily dose of opioid by 50-100% for moderate to severe pain
- Long-acting, sustained-release opioids can be increased every 24 hours (with the exception of transdermal fentanyl and methadone)

Methadone

- Should only be prescribed/adjusted by provider with adequate training and experience
  - Advantages:
    - Rapid onset of analgesia
    - Effective for neuropathic pain
    - Chemically unrelated to other opioids
    - No active or toxic metabolites
    - Available in many dosage forms
    - Lower incidence of neurotoxic adverse effects

Opioid Rotation

- Lack of therapeutic response
- Development of adverse effects
  - GI effects
  - Autonomic
  - Cutaneous
  - CNS
  - True opioid allergy
- Change in patient status
Equianalgesic Opioid Dosing

<table>
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<tr>
<th>DRUG</th>
<th>PARENTERAL</th>
<th>ORAL</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.1</td>
<td>0.4 (SL)</td>
</tr>
<tr>
<td>Codeine</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10*</td>
<td>20</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100*</td>
<td>120</td>
</tr>
</tbody>
</table>


Compliance with Opioids

- Fear of addiction
- Fear of tolerance
- Opioid toxicity
- The “good” patient
- Meaning of pain
- Caregiver administration barriers

Patient/Family Education

Addiction vs. Dependence

- Physical dependence
  - Development of a withdrawal syndrome when a drug is suddenly discontinued or an antagonist is administered
- Psychological dependence
  - Overwhelming involvement with the acquisition and use of a drug, characterized by: loss of control, compulsive drug use, and use despite harm
- Tolerance
  - The need to increase a drug to achieve the same effect
Corticosteroids

- **Uses**
  - Anorexia/cachexia, adjunct pain med, weakness/fatigue
- **Benefits**
  - May be able to decrease opioid use, appetite stimulation, increased energy
- **Side effects**
  - Muscle wasting, osteoporosis, diabetes, insomnia, agitation, psychosis

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Patient Case

- On initial assessment, Olive has complaints of pain in her left hip and lower back. She also complains that she doesn’t have enough energy to get through the day and she is tired of eating spinach. She is started on dexamethasone 4mg by mouth once daily and morphine liquid 5mg (0.25mL) PO Q 4hrs PRN severe pain
- Follow-up visit later that week, she reports functional improvement in pain, using 3-4 doses of morphine 5mg per day, but excessive itching with no signs of rash
- What do you advise?

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V.O.M.I.T.

- Vestibular
- Obstruction of bowel
- Motility of upper GI
- Infection/Inflammation
- Toxins (opioids, chemo, electrolytes)
Nausea/Vomiting Pathway

**Drug-induced Constipation**
- Dose related side effect
- Meds most likely to cause constipation:
  - Antispasmodics
  - Antihistamines
  - Antidepressants
  - Diuretics
  - Aluminum antacids
  - Opioids

**Management**
- Initiate prophylactic bowel regimen including stool softener AND stimulant laxative
- Avoid bulk forming laxatives in dehydrated patients
- Nonpharmacologic therapies
  - Prune juice, fruit paste
  - Stimulate bowel with warm fluids during and after meals
Dyspnea

- Defined as a discomfort in breathing
  - Common symptom in advanced cancers and other advanced illnesses (e.g. CHF, COPD, AIDS)
- Subjective sensation influenced by physical, psychological, social, and spiritual factors
  - Assessment based on subjective responses; no place for objective findings such as CXR, lab tests, oximetry
- Pathophysiology
  - Physical respiratory impedance – pleural effusions, PE, increased secretions, pneumonia, COPD, weakness in respiratory muscles
  - Chemical causes – hypercapnia, hypoxia
  - Neuromechanical dissociation – mismatch between what the brain expects as respiration and signals it receives

Dyspnea - Treatment

- Non-pharmacologic
  - Re-positioning (avoid lying flat), maintain cool room temps, relaxation exercises, acupuncture, minimal exertion
- Pharmacologic
  - Oxygen therapy for documented hypoxia esp. COPD
  - Opioids – first-line treatment
    - No optimal agent or dose although nebulized route not shown to be superior; consider opioid naïve vs. opioid-tolerant patient
    - Morphine most commonly used
    - Rescue doses at 30-50% of scheduled dose typically effective
  - Anxiolytics
    - Benzodiazepines reserved for breakthrough or refractory dyspnea compounded by anxiety or when ADRs limit titration of opioids to efficacy

Anxiety/Restlessness

- Benzodiazepines most commonly used
- Additional benefits with SSRIs, TCAs, anticonvulsants
- Can be associated with breathlessness
### Benzodiazepine Equivalents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Equivalent Doses</th>
<th>Active Metabolites</th>
<th>Onset</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Diazepam (Valium)</td>
<td>5 mg</td>
<td>+++</td>
<td>Rapid</td>
<td>Long</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>1 mg</td>
<td>-</td>
<td>Intermediate Intermediate</td>
<td></td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>15 mg</td>
<td>-</td>
<td>Intermediate Intermediate</td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td>10 mg</td>
<td>-</td>
<td>Intermediate Intermediate</td>
<td></td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.5 mg</td>
<td>+</td>
<td>Intermediate Short</td>
<td></td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.25 mg</td>
<td>-</td>
<td>Rapid</td>
<td>Long</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>25 mg</td>
<td>+++</td>
<td>Intermediate Long</td>
<td></td>
</tr>
</tbody>
</table>

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### Delirium/agitation

- Identify/remove precipitating factors
- Antipsychotics are treatment of choice
- First generation vs. second generation
- Haloperidol generally preferred agent
  - Ease of administration
  - Variable dosing
- Benzodiazepines can worsen delirium

### Comparative Adverse Effects of Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Sedation</th>
<th>Anti-cholinergic side effects</th>
<th>Extrapyramidal symptoms</th>
<th>QTc prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chlorzepine</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

UpToDate 2015. Table not all inclusive.
Drying Up Secretions

- Tertiary amines
  - Scopolamine, atropine, hyoscyamine
  - Cross blood-brain barrier (BBB) and can cause sedation, delirium
- Quaternary amines
  - Glycopyrrolate – does not cross BBB
- Consider onset of action
  - Scopolamine ~ 12 hours
- Ease of administration
  - Atropine ophthalmic drops

Anticholinergic Effects

- Peripheral
  - Dry eyes
  - Urinary retention
  - Dry mouth
  - Constipation
  - Heat intolerance
  - Tachycardia
  - Decreased sweating
- Central
  - Forgetfulness
  - Agitation/confusion
  - Delirium
  - Paranoia
  - Dizziness
  - Drowsiness
  - Falls

Drugs that Cause Anticholinergic Effects*

- Oxybutynin
- Benztrapine
- Scopolamine
- Diphenoxylate
- Hyoscyamine
- Atropine
- Ipratropium
- Diphenhydramine
- Tricyclic antidepressants
- Chlorpromazine
- Prochlorperazine
- Promethazine
- Cyclobenzaprine

*List not all-inclusive
Management

- Assess risk vs. benefit of adding anticholinergic medication
- Choose alternative medication when possible
- Consider nondrug therapy when appropriate
- Use the lowest, effective dose for the shortest duration
  - Cumulative effect of anticholinergics

Dysphagia

- Can be associated with odynophagia and/or aspiration
- Occurs regularly in patients with advanced disease, especially in the setting of neurologic disease
  - ALS and other motor neuron diseases, brain metastases, leptomeningeal carcinomatosis, head/neck CA
- Medication administration

Medication Dosage Forms

- Liquid – PO, SL
  - Buccal absorption dependent on lipophilicity of drug
    - Fentanyl > methadone > hydromorphone > oxycodone > morphine
    - 20% avg absorption of morphine 5 mg dose after 10 minutes
- Injection – IV, SC
- Suppository – including oral formulations
- Topical gel – local absorption
- Transdermal

Injectable Medications – IV, SC

- Advantages
  - Quick onset of action
  - Effective
  - Essential medications available
- Disadvantages
  - High caregiver burden
  - High cost
  - Difficulty obtaining medication/delays
  - May not be available as injectable
  - Complications
  - Decreased peripheral circulation

Rectal Suppositories

- Advantages
  - Effective absorption
  - Versatility in medications
  - May be inexpensive
- Disadvantages
  - High caregiver burden
  - Discomfort for patient
  - May be expensive if compounded
  - Limited doses
  - Delayed onset of action

Transdermal Administration

- Advantages
  - Generally easy and comfortable for patient
- Disadvantages
  - Delayed onset of action
  - Potential for erratic absorption
  - Cost
  - Limited medications
  - Lack of breakthrough medication
Patient Case

- Mrs. Oyl has been managed at home for 2 months with oxycodone 10mg PO Q6hrs scheduled and dexamethasone 4mg PO BID
- She begins to experience dysphagia and can no longer swallow the pills
- What are some options for pain management at this point?

Symptom Management Summary

- Use frequent, standard assessment
- Oral medications when possible, altering the route as needed
- Assess for medication side effects; anticipate and treat as necessary
- Address possible reversible contributing causes
- Discontinue medications no longer contributing to symptom control

Questions?

Contact Information:

Traci White, PharmD, PhC
Pharmacist Clinician, Mesilla Valley Hospice
Assistant Professor, UNM College of Pharmacy
tmwhite@nmsu.edu