Hospice Pharmacotherapy 101: Symptom Management for Anxiety, Depression, Agitation, and Insomnia

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Clinical Pharmacist

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.
### Objectives

- Review pathophysiology and assessment of common psychiatric symptoms in end of life
- Discuss non-pharmacologic and pharmacologic treatment of common psychiatric symptoms in end of life
- Develop a plan for addressing psychiatric symptoms based on clinical presentation and patient-specific goals of care

### Patient Case: Mrs. A

45 year old female admitted to hospice with recurrent breast cancer and lung metastases. The tumor in her breast can be palpated inside her right axilla. Patient is the primary care provider 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
- Dexamethasone 4mg by mouth qAM
- Morphine ER (MS CONTIN®) 15mg by mouth q8h ATC
- Morphine sulfate 20mg/ml solution 5mg by mouth q4h prn breakthrough pain
Anxiety

Anxiety – Prevalence and Background

• Prevalence not well studied, but reported to be 21-23% in palliative care patients

• Many conditions and medications can precipitate anxiety

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired physical activity</td>
<td>Albuterol</td>
</tr>
<tr>
<td>Decreased social life</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Loss of independence</td>
<td>Pseudoephedrine</td>
</tr>
<tr>
<td>Uncontrolled symptoms</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
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<tr>
<td>Drug withdrawal states</td>
<td></td>
</tr>
</tbody>
</table>
Anxiety - Characteristics

• Exaggerated worry, tension and irritability that appear to have no cause or are more intense than the situation warrants

• Physical signs:
  – Restlessness
  – Headaches
  – Sweating
  – Trembling
  – Muscle twitching or tension
  – Dyspnea
  – Insomnia

Anxiety - Non-pharmacologic Treatment

• Treat underlying cause if appropriate
  – Ex. Decreased social life

• Psychotherapeutic support
  – Incorporate interdisciplinary team including social workers, spiritual care counselors and psychologists
  – Techniques:
    • Simple relaxation exercises
    • Distraction strategies
• History of effective treatments?

• **Aim to prevent anxiety**, not just treat flare-ups

• Pain management analogy:
  – Scheduled medication + PRN orders

• **Start low and titrate up as needed**

• Assess for underlying depression
  – If life expectancy > 2-3 months, add serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)?

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### Benzodiazepines for Anxiety

<table>
<thead>
<tr>
<th>Medication</th>
<th>Approximate Equivalent Dose (mg)</th>
<th>Usual Dosing Regimen</th>
<th>Peak Effect (PO)</th>
<th>Available Routes of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam (Ativan®)</td>
<td>1</td>
<td>0.5mg Q6h</td>
<td>2-4 hrs</td>
<td>PO, SL, PR, IV, SQ, IM</td>
</tr>
<tr>
<td>Alprazolam (Xanax®)</td>
<td>0.5</td>
<td>0.25mg Q6h</td>
<td>1-2hrs</td>
<td>PO, SL, PR</td>
</tr>
<tr>
<td>Diazepam (Valium®)</td>
<td>5</td>
<td>5mg Q8h</td>
<td>0.5-2hrs</td>
<td>PO, SL, PR, IV, IM</td>
</tr>
</tbody>
</table>
Considerations for Mrs. A

1. Would you be concerned about anxiety in this patient?
   A. Yes
   B. No

2. What, if any, therapies would you initiate for the patient?
   A. Lorazepam 0.25mg PO Q4H prn anxiety
   B. Diazepam 10mg PO BID and Q4H prn anxiety
   C. Citalopram 20mg daily
   D. None at this time
Considerations for Mrs. A

1. Would you be concerned about anxiety in this patient?
   A. Yes
   B. No

2. What, if any, therapies would you initiate for the patient?
   A. Lorazepam 0.25mg PO Q4H prn anxiety
   B. Diazepam 10mg PO BID and Q4H prn anxiety
   C. Citalopram 20mg daily
   D. None at this time

Depression
Depression – Prevalence and Background

• Clinical depression is estimated between 20-50%

• Clinical depression is a complication of life-limiting illness and extends beyond the phase of adaptation to loss in the **grieving process**

• Potential causes or contributors to depression symptoms include:
  – Untreated symptoms (pain, anxiety, nausea, etc)
  – Spiritual concerns
  – Sudden loss or receiving bad news

Depression – Characteristics

• Clinical features of a depression episode include **depressed mood** and the following symptoms (SIG-E-CAPS):
  – Sleep disturbance
  – Interest/pleasure reduction
  – Guilty feeling or thoughts of worthlessness
  – Energy change/fatigue
  – Concentration impairment
  – Appetite/weight change
  – Psychomotor retardation or agitation
  – Suicidal thoughts

• Asking **“Are you depressed?”** may be a sufficient depression screening

• Inquire about presence of suicidal thoughts or intent in patient with signs or symptoms of depression
• Semi-Psychotherapeutic techniques
  – Incorporate interdisciplinary team including social workers, spiritual care counselors and psychologists
  – Examples: dignity therapy, short-term life review, life completion discussions

• Cognitive-behavioral techniques
  – Relaxation
  – Music therapy
  – Art therapy

Depression - Non-Pharmacological Treatment

• Treatment modalities based on the patient’s prognosis
  - **Shorter prognosis** (less than 4-6 weeks)
    • Drug of choice: Stimulants (off-label indication)
  
<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (Ritalin®)</td>
<td>2.5-10mg BID</td>
<td>Tabs, chewable tabs, oral solution</td>
</tr>
</tbody>
</table>
  
  (usually 8AM and 12PM)

  - **Longer prognosis** (greater than 4-6 weeks)
    • Drugs of choice: Serotonin reuptake inhibitors (SSRIs)
    - Less risk of side effects compared to tricyclic antidepressants (TCAs)
    - Onset of action generally 4-6 weeks
    - All can lower seizure threshold

Depression - Pharmacological Treatment
### Serotonin Reuptake Inhibitors (SSRIs)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Dosage Forms</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>10-20mg daily</td>
<td>Tabs, caps, oral solution</td>
<td>• Half-life 4-6 days</td>
</tr>
<tr>
<td>(Prozac®)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sertraline</td>
<td>25-50mg daily</td>
<td>Tabs, oral solution</td>
<td></td>
</tr>
<tr>
<td>(Zoloft®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>10-20mg daily</td>
<td>Tabs, oral solution</td>
<td>• &gt; 60 yoa: max dose 20mg/day due to increased risk of QT prolongation</td>
</tr>
<tr>
<td>(Celexa®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5-10mg daily</td>
<td>Tabs, oral liquid</td>
<td></td>
</tr>
<tr>
<td>(Lexapro®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10mg daily</td>
<td>Tabs, oral suspension</td>
<td>• Highest risk of anticholinergic effects</td>
</tr>
<tr>
<td>(Paxil®)</td>
<td></td>
<td></td>
<td>• Withdrawal symptoms with missed doses due to short half-life</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30mg daily</td>
<td>Caps</td>
<td>• Indication for depression and neuropathy</td>
</tr>
<tr>
<td>(Cymbalta®)</td>
<td>(30-60mg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Depression - Monitoring

- Monitor depressed patients for development of suicidal ideation or intent  
  - FDA boxed warning for antidepressants
- Symptom improvement
  - **Week 1**: decreased agitation/anxiety, improved sleep and appetite
  - **Week 1-3**: improved activity, concentration, thinking and self-care
  - **Week 2-4**: improved mood, return of pleasure, decreased hopelessness
Depression – Suboptimal Treatment Response

- **Patient tolerating and below therapeutic dose range**
  - Consider increasing dose of anti-depressant (AD)

- **Within therapeutic dose range of newly initiated AD**
  - Assess patient safety and prognosis
  - Monitor response over 6-8 weeks
  - Maintain current dose

- **Adequate trial (6-8 weeks) on current regimen**
  - Changing medication within same/different AD class
  - Obtain psychiatric consult for combination/augmentation therapies

Considerations for Mrs. A

1. **Would you be concerned about depression in this patient?**
   - A. Yes
   - B. No
Considerations for Mrs. A

1. Would you be concerned about depression in this patient?
   A. Yes
   B. No

2. What, if any, therapies would you initiate for the patient?
   A. Fluoxetine 10mg by mouth daily
   B. Psychosocial support
   C. None
Agitation – Prevalence and Background

- Delirium is estimated to occur in more than 80% of all terminally ill patients prior to death
- Agitation is a component of delirium in approximately 46% of patients
- Etiology is multifactorial
Potentially Reversible Causes of Delirium

- Urinary retention
- Constipation
- Hypoxemia
- Infection
- Metabolic abnormalities
  - ↑ or ↓ sodium
  - ↑ calcium
  - Altered blood glucose
- Dehydration
- Fatigue, sleep deprivation, altered circadian rhythms
- Severe anemia
- Nutritional deficiencies
  - Thiamine, folate, B12
- Drug and alcohol withdrawal
- Pain (especially uncontrolled)

Agitation/Delirium – Characteristics

**Agitation**
- An unpleasant state of extreme arousal, increased tension and irritability
- Extreme agitation can lead to confusion, hyperactivity, and hostility
- Agitation can have a **gradual or sudden onset**
  - May last minutes to weeks or months
- Pain, stress and fever can all increase agitation

**Delirium**
- **Alterations in consciousness and attention** associated with:
  - Cognitive (e.g. amnesia), behavioral (e.g. agitation), perceptual disturbances (e.g. hallucinations)
- Other clinical features:
  - Sleep-wake cycle disturbance (diurnal disruptions)
  - Delusions
  - Emotional lability
  - Psychomotor activity disturbances
Assess for and if appropriate, treat reversible causes of delirium and agitation.

Take Note!

Delirium - Non-Pharmacological Treatment

• Environmental control
  – Sound, lighting, stimuli
  – Frequent reorientation

• Psychosocial support
  – Family, friends, counselors

• Distraction
  – Relaxation, massage, music

• Adequate sleep
Delirium - Treatment

- If appropriate, treat reversible causes
  - Individualized approach based on patient’s goals of care

- Reduce, eliminate, or change drugs that may be contributing to delirium

- Use hypnotic medication to provide adequate sleep

- Use antipsychotic drugs to treat confusion
  - Neuroleptics (antipsychotics) off label use
    - Haloperidol (Haldol®), chlorpromazine (Thorazine®)
    - Olanzapine (Zyprexa®), quetiapine (Seroquel®), and risperidone (Risperdal®)

- Add benzodiazepines only if needed for anxiety and/or restlessness

Antipsychotic Agents

- May help with agitation, hallucinations, and aggression

- FDA Black Box warning in elderly patients with dementia
  - Increased mortality compared to placebo

- Always start at low end of dosing range
### Antipsychotic Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Approximate Equivalent Dose (mg)</th>
<th>Usual Dosage Regimen</th>
<th>Available Routes of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>1</td>
<td>0.5mg PO BID</td>
<td>PO, SL, PR, IM, SQ, IV</td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine®)</td>
<td>50</td>
<td>25mg PO BID</td>
<td>PO, SL, PR, IM, IV</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa®)</td>
<td>2.5</td>
<td>2.5mg PO Daily</td>
<td>PO</td>
</tr>
<tr>
<td>Quetiapine (Seroquel®)</td>
<td>50</td>
<td>50mg PO Daily</td>
<td>PO</td>
</tr>
<tr>
<td>Risperidone (Risperdal®)</td>
<td>1</td>
<td>0.5mg PO BID</td>
<td>PO, SL</td>
</tr>
</tbody>
</table>

### Antipsychotic Agent Comments

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<thead>
<tr>
<th>Antipsychotic Agent</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>Least sedating antipsychotic; treats nausea/vomiting; AVOID in Parkinson’s Disease and Lewy Body Dementia</td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine®)</td>
<td>FDA indication for hiccups; Other uses: headache in brain cancer; Tenesmus; Nausea/vomiting; May cause orthostatic hypotension in ambulatory patients; AVOID in Parkinson’s Disease and Lewy Body Dementia</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa®)</td>
<td>Potential for lipid &amp; glucose abnormalities; Sedating</td>
</tr>
<tr>
<td>Quetiapine (Seroquel®)</td>
<td>Potential for lipid &amp; glucose abnormalities; Sedating; PREFERRED in Parkinson’s Disease and Lewy Body Dementia</td>
</tr>
<tr>
<td>Risperidone (Risperdal®)</td>
<td>Potential for lipid &amp; glucose abnormalities; Sedating</td>
</tr>
</tbody>
</table>
Considerations for Mrs. A

1. Which of the following could contribute to the development of delirium in this patient?
   A. Opioid regimen
   B. Continuation of medications for diabetes
   C. Cerebral disease
   D. All of the above

2. What actions can we ensure are occurring for the patient to reduce risk of delirium?
   A. Regularly monitor blood glucose levels, discontinue therapy when no longer indicated
   B. Prevent and treat constipation
   C. Monitor pain control
   D. All of the above
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   D. All of the above

2. What actions can we ensure are occurring for the patient to reduce risk of delirium?
   A. Regularly monitor blood glucose levels, discontinue therapy when no longer indicated
   B. Prevent and treat constipation
   C. Monitor pain control
   D. All of the above

Considerations for Mrs. A

Insomnia
• Prevalence not well studied, but reported to be as high as 70%

• Insomnia is the occurrence of difficulty with initiating or maintaining sleep 3 or more days per week that results in impaired daytime function

• Potential causes or contributing factors to insomnia include:
  – Untreated physical symptoms (pain, anxiety, nausea, etc)
  – Other psychological disorders include insomnia in diagnostic criteria
  – Medications (caffeine, corticosteroids, diuretics, nicotine)

• Insomnia symptoms:
  – Difficulty with sleep initiation
  – Decreased duration of sleep intervals
  – Early morning wakening

• Patient may appear to sleep an adequate duration but sleep may not be restful or restorative

• Assess for barriers to sleep
  – New location/caregiver
  – Noise
  – Uncontrolled symptoms
  – Fearful of dying/Loneliness
  – Sleep apnea
  – Restless leg
  – Medications
  – Depression
Insomnia - Non-Pharmacological Treatment

- **Sleep hygiene**
  - Appropriate surroundings
  - Quiet atmosphere
  - Limit caffeine/alcohol

- **Sleep restriction**
  - Limit daytime naps
  - Set realistic bedtimes

- **Stimulus control**
  - Reducing time spent in bed awake

- **Cognitive therapy**
  - Control pre-sleep thoughts
  - Relaxation strategies

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Insomnia - Pharmacological Treatment

- Assessment of sleep disturbance can be helpful to choose therapy

- **Sleep onset** (falling asleep) difficulty
  - May benefit from shorter-acting agent
    - Ex. lorazepam

- **Maintenance** (staying asleep) difficulty
  - Evaluate for possible causes of wakening
  - May benefit from a longer-acting agent
    - Ex. trazodone

- **Circadian rhythm dysfunction** (biological daily cycle)
  - Common in neurocognitive disorders or blindness
  - May benefit from melatonin
Benzodiazepines for Insomnia

- Avoid duplications of therapy (multi-symptom therapy)
- May worsen symptoms of delirium

<table>
<thead>
<tr>
<th>Medication</th>
<th>Approximate Equivalent Dose (mg)</th>
<th>Usual Dosing Regimen</th>
<th>Available Routes of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam (Ativan®)</td>
<td>1</td>
<td>0.5mg QHS</td>
<td>PO, SL, PR, IV, SQ, IM</td>
</tr>
<tr>
<td>Temazepam (Restoril®)</td>
<td>30</td>
<td>15mg QHS</td>
<td>PO</td>
</tr>
</tbody>
</table>

Benzodiazepine-like Medications

- The Zs
  - Produce hypnotic effects similar to benzodiazepines
  - No clear advantage over benzodiazepines
  - Less anxiolytic and anticonvulsant effects
  - Short duration of action of 4 to 6 hours
  - More effective for sleep onset

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dosing Regimen</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem (Ambien®)</td>
<td>5-10mg QHS</td>
<td>Tablets</td>
</tr>
<tr>
<td>Zaleplon (Sonata®)</td>
<td>5-10mg QHS</td>
<td>Capsules</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta®)</td>
<td>1mg QHS</td>
<td>Tablets</td>
</tr>
</tbody>
</table>
Antidepressants for Insomnia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dosing Regimen</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone (Desyrel®)</td>
<td>25-100mg QHS</td>
<td>Tablet</td>
</tr>
<tr>
<td>Mirtazapine (Remeron®)</td>
<td>7.5-15mg QHS</td>
<td>Tablet</td>
</tr>
<tr>
<td>Doxepin (Silenor®)</td>
<td>3-6mg QHS</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

• Multi-symptom therapy?

Take Note!

• Pay attention to side effect profiles of medications and use them to the advantage
Antipsychotics for Insomnia

- Typical/Atypical Agents
  - Off-label use
  - Not first line agents, unless psychiatric condition or symptoms present

- Quetiapine
  - Commonly prescribed for sleep disturbances
  - Depression, bipolar, schizophrenia FDA indications
  - Modest improvement in total sleep time (TST) ~20-40min
  - Side effects: Daytime sleepiness, agitation, dry mouth, CVA
  - Not enough evidence to recommend first line unless also treating psychiatric symptoms
    - Insomnia not an acceptable use of quetiapine for patients in LTC facilities
    - Citation risk F329

Patient Case: Mrs. A

45 year old female on hospice with recurrent breast cancer and lung metastases. Patient is primary care provider for 2 children under the age of 10, and has a supportive husband who works full time outside of their home.

Current complaint: Patient is complaining of difficulty sleeping at night. Occurring for about a week. Pain is controlled well.

Medications:

- Glucophage (Metformin®) 1000mg by mouth twice daily
- Glucotrol (Glipizide XL®) 10mg by mouth every morning
- Dexamethasone 4mg by mouth qAM
- Morphine ER (MS CONTIN®) 15mg by mouth q8h ATC
- Morphine sulfate 20mg/ml solution 5mg by mouth q4h prn breakthrough pain
- Lorazepam 0.25mg by mouth q4h prn anxiety
Patient Case: Mrs. A

- Goals: to remain as alert as possible during the day, sleep well at night, have energy to interact with children and husband

- What information would be beneficial to determine appropriate medication therapy for treating insomnia?

  A. Are you having trouble falling asleep or staying asleep?
  B. What is causing your anxiety?
  C. Are you feeling depressed?

Patient Case: Mrs. A

- Goals: to remain as alert as possible during the day, sleep well at night, have energy to interact with children and husband

- What information would be beneficial to determine appropriate medication therapy for treating insomnia?

  A. Are you having trouble falling asleep or staying asleep?
  B. What is causing your anxiety?
  C. Are you feeling depressed?
Patient Case: Mrs. A

- The patient states she is having trouble falling asleep because she feels overwhelmed and anxious before bed.

- What medication regimen would you initiate?

  A. Trazodone 50mg QHS  
  B. Lorazepam 0.5mg QHS  
  C. Zolpidem 5mg QHS

- What non-pharmacologic treatment options would you suggest?
Aim is to prevent anxiety which may require scheduling medication doses throughout the day

The pharmacologic treatment regimen for depression depends on the patient's prognosis

Assess for and if appropriate, treat reversible causes of delirium and agitation.

Determine if patient is having trouble falling asleep or staying asleep to choose appropriate regimen for relieving insomnia

Questions?

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References


References