Pharmacotherapy of Insomnia, Anxiety and Depression in Older Adults

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Anxiety and Depression

- Anxiety disorders occur in about 10% of the geriatric population.
- 10-20% of community dwelling elderly are diagnosed with depression.
- 60-90% of patients with GAD also have concurrent depression.
- The most common co-morbid disorder is depression.
### Medications Which can Contribute to Symptoms of Anxiety and Depression

#### Anxiety
- Decongestants
- Beta agonists
- Bupropion
- Fluoxetine
- Stimulants
- Steroids
- Caffeine

#### Depression
- Beta blockers
- Clonidine
- BZD’s
- Finasteride
- Progesterone
- Sedating antihistamines
- Muscle relaxants
- Steroids
- Narcotics
- Indomethacin
- Calcium Channel Blockers
Treatment of Anxiety Disorders

- Benzodiazepines
  - Most effective and fastest acting anti-anxiety medications
  - Increased risk of falling, cognitive impairment
  - Maybe used short term if symptoms are severe
  - Start an SSRI/SNRi concurrently
  - DC BZD when the anti-depressant kicks in
## Medications Used for Anxiety

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg)</th>
<th>PK</th>
<th>Side effects</th>
<th>Geriatric Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>Start with 0.25mg and titrate up slowly</td>
<td>T1/2 up to 40 hrs Peak Onset 1-4 h</td>
<td>Sedation, dizziness, mental status changes</td>
<td>LONG acting BZD Risk of falling, confusion</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Start with 0.25mg and titrate up slowly</td>
<td>T1/2 10-20 hr Peak Onset 1-1.5hr Not effected by age</td>
<td>Sedation dizziness, Mental status changes</td>
<td>Risk of falling, confusion</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Start with 0.25mg and titrate up slowly</td>
<td>T1/2 6-20 hrs Peak Onset 30 min-1.5hr</td>
<td>Sedation, dizziness mental status changes</td>
<td>Risk of falling confusion</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5-60</td>
<td>Dosed bid or tid</td>
<td>GI, Dizziness, Weight changes, sexual dysfunction, bleeding</td>
<td>Must be dosed on a schedule. Similar to SSRI’s. Takes 4-6 weeks for full effect</td>
</tr>
</tbody>
</table>
Selective Serotonin Reuptake Inhibitors$^{3,8,12,14}$

**Advantages**
- Better tolerated than previous classes
- Less lethal than TCAs in cases of overdose
- STAR*D trial showed that patients who do not respond to 1 SSRI may respond to another
- Weekly formulation of fluoxetine

**Disadvantages**
- Agitation/anxiety during early phase of therapy
- Anticholinergic properties (paroxetine)
- Dose related conduction effects (citalopram + escitalopram)
- SIADH/hyponatremia
- Common adverse effects:
  - GI complaints
  - Insomnia
    - Fluoxetine, sertraline, vilazodone
  - Sedation
    - Paroxetine, fluvoxamine
  - Sexual dysfunction
Serotonin Norepinephrine Reuptake Inhibitors\textsuperscript{3,12}

- **Advantages**
  - “Dual action” may be beneficial for treatment non-responders
  - Less lethal than TCAs in cases of overdose
  - Other uses:
    - Peripheral neuropathy
    - Fibromyalgia
    - Chronic musculoskeletal pain

- **Disadvantages**
  - Similar adverse effect profile as SSRIs
  - Dose-related hypertension
  - SIADH/hyponatremia
SSRIs and SNRIs for Anxiety

- SSRIs are considered the treatment of choice for anxiety
- Citalopram, Escitalopram, or Sertraline
  - Better Side effect profile
  - Fewer drug interactions
- Paroxetine
  - May be more sedating than the others, but more anticholinergic
- SNRI Effexor was the 1\textsuperscript{st} anti-depressant to be FDA approved for anxiety

- Treatment of anxiety takes 4-6 weeks before efficacy can be seen
Trazodone

- Mechanism of action = serotonin reuptake inhibitor that also blocks serotonin-2A receptors
- Advantages
  - Lacks anticholinergic or cardiotoxic effects
  - Often used for insomnia
- Disadvantages
  - Orthostatic hypotension, sedation
  - Priapism = rare (0.1% or less)
Bupropion

• Mechanism of action = inhibits reuptake of dopamine + norepinephrine

• Advantages
  – May improve sexual function
  – Other indications = smoking cessation, ADHD

• Disadvantages
  – Increased risk of seizures
    • Minimized by:
      – Avoid in susceptible patients (Seizure, Eating disorder, Brain injury)
      – Avoid rapid dosage titration
      – Avoid >150 mg/dose or 450 mg/day (IR), 400 mg/day (SR), 450 mg/day (ER)
  – Common adverse effects
    • Anxiety, insomnia, decreased appetite, headache
Mirtazapine

- Mechanism of action = inhibits presynaptic alpha2-autoreceptors → ↑ serotonin + norepinephrine
  - Blocks serotonin-2A, serotonin-3, + serotonin-2C receptors

- Advantages/disadvantages
  - Sedative effect
    - Lower doses = sedating vs. higher doses = insomnia
  - ↑ appetite + weight
## Selected Drugs Which can be Safely Used in Geriatrics for Anxiety and Depression

<table>
<thead>
<tr>
<th>Class</th>
<th>Dose (mg)</th>
<th>Side effects</th>
<th>Considerations</th>
<th>Used for anxiety?</th>
</tr>
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<tbody>
<tr>
<td><strong>SSRI’s</strong></td>
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<tr>
<td>Sertraline</td>
<td>25-200</td>
<td>Bruising/Bleeding; GI, Weight changes; Anxiety/insomnia/sedation; Low Na; Falls/hypotension Sexual dysfunction</td>
<td>Prozac: long half life Activating QT prolongation Paxil: Some anticholinergic activity</td>
<td>Yes for all except fluoxetine</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10-40</td>
<td></td>
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<td></td>
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<tr>
<td>Citalopram</td>
<td>10-20</td>
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<tr>
<td>Escitalopram</td>
<td>5-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10-60</td>
<td></td>
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<tr>
<td><strong>SNRI’s</strong></td>
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<tr>
<td>Venlafaxine</td>
<td>37.5-225</td>
<td>Same as SSRI’s Hypertension</td>
<td>At higher doses NE effect with Effexor Liver disease Renal insufficiency</td>
<td>YES</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>20-120</td>
<td></td>
<td></td>
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<tr>
<td>Desvenlafaxine</td>
<td>25-50</td>
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<tr>
<td><strong>NDRI</strong></td>
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<tr>
<td>Bupropion</td>
<td>150-450</td>
<td>Anxiety, insomnia, weight loss, nausea, diarrhea, agitation</td>
<td>Seizures; Helpful in smoking cessation and ADHD</td>
<td>NO</td>
</tr>
<tr>
<td><strong>NE Blocker/5HT</strong></td>
<td></td>
<td>Sedation, weight gain, dizziness</td>
<td>Lower doses are more sedating</td>
<td>Not FDA approved, but may be helpful</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7.5-45</td>
<td></td>
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</table>
Insomnia is Common in Seniors and has Many Consequences

• Prevalence
  – 6-18% of the general population\(^1\)
  – 57% of persons age 65+\(^2,3\)

• Costs
  – $30-35 billion annually in direct & indirect costs\(^4\)

• Consequences:
  – Daytime dysfunction, decreased quality of life, psychiatric disorders, falls, increased mortality\(^5\)

Normal Stages of Sleep

- **Stage I**
  - Mental relaxation/eyes closing; 5-30min
- **Stage II**
  - Disconnect from the outside world; can’t hear noise; 50% of total sleep time
- **Stage III-IV:** Deep sleep: 15-20%
  - III 20-50% delta waves/IV all delta waves
- **REM sleep:** dreaming
Sleep Changes in Ageing\textsuperscript{6}

Compared to Young Adults

- Stage I: takes longer to fall asleep
- Stage II: Impaired, easily awakened
- Stage III and IV: Shorter in older patients
- REM: Shorter in older patients

What effect do Hypnotics have on Sleep Cycle?

- Shorten stage I: faster sleep onset
- Extend stage II: More time spent in less deep sleep
- Shorten Stage III and IV: Less deep restorative sleep
- Shorten REM: Less dreaming
Non-Drug Therapy is Effective

- Meta-analysis of 23 randomized trials of cognitive-behavioral treatment, relaxation, and behavioral treatment (sleep hygiene education)\(^7\)
  - Increased:
    - Sleep efficiency
    - Sleep quality
  - Decreased:
    - Sleep latency
    - Wake time after sleep onset
  - Did not compare individual forms of non-pharmacologic therapies.

Principles of Sleep Hygiene

- Regular schedule
- Go to bed only when sleepy
- Cover the Alarm Clock
- Avoid long naps
- Don’t toss and turn
- Regular exercise/outdoor time
- Avoid large meals at night
- Limit Caffeine and Alcohol

- Comfortable bed/pillows/blankets
- Using the bedroom for sex and sleep only
- Comfortable temperature
- No lights on at night
- Relax before going to bed
- Melatonin/L-tryptophan rich food
Caffeine Content in Certain Products

- Coffee, brewed: 8 oz. = 133mg (range: 102-200 mg) (16 oz. = 266 mg)
- Starbucks Brewed Coffee: (Grande) 16 oz. = 320 mg
- Tea, brewed: 8 oz. = 53mg (range: 40-120)
- Starbucks Chai Tea Latte: (Grande) 16 oz. = 100 mg
- Snapple, Lemon (and diet version): 16 oz. = 42 mg
- Diet Coke: 12 oz. = 47mg (20 oz. = 78mg)
- Pepsi: 12 oz. = 38 mg; (20 oz. = 63 mg)
- Mountain Dew, regular or diet: 12 oz. = 54 mg (20 oz. 90 mg)
- Ben & Jerry's Coffee Heath Bar Crunch: 8 oz. = 84 mg
- Hot Cocoa 8 oz. = 9 mg (range: 3-13)
Medications which Contribute to Insomnia

- Diuretics
- Dopamine agonists
- Antidepressants
- Thyroid replacement
- HRT
- Stimulant Herbal Supplements

- Some anti-psychotics
- Dementia Medications
- Steroids
- Decongestants
- Beta agonists
- Appetite suppressants
- ADHD medications
Medications Replace Sleep Hygiene Education as First-Line Treatment

- Primary care teams lack time & resources to provide sleep hygiene education
- Medication therapy frequently used despite drawbacks
  - Beers List:
    - Antihistamines (diphenhydramine, doxylamine) Watch out for combination products
      - Tylenol PM, Advil PM, cough and cold syrups
    - Benzodiazepines: (temazepam, lorazepam, alprazolam)
    - Non-benzodiazepines (zolpidem Ambien, zaleplon (Sonata), eszopiclone (Lunesta))
    - TCA's
  - Others associated with next-day sedation and dizziness
    - Gabapentin, quetiapine, trazodone
Sedative-Hypnotic Use Harmful in Seniors

- Meta-analysis of 24 RCTs evaluated all sedative-hypnotic use in 2,417 patients age 60+\textsuperscript{8}
- Number needed to harm: 6 (95% CI 4.7-7.1)
- Number needed to treat: 13 (95% CI 6.7-62.9)
- Side Effects observed: Drowsiness, fatigue, headache, nightmares, nausea, loss of balance, dizziness, falling, MVA’s broken bones, drowsiness in the AM

A Meta Analysis of Risks and Benefits of BZD’s and BZD-like Drugs

- 8 studies of 601 pts increase in sleep time was 25.2 min
- 8 studies of 524 pts BZD vs placebo, increase in sleep time was 34.2 min
- 6 studies of 441 pts mean # of awakenings decreased by 0.63
- 6 studies of 296 pts BZD vs placebo mean # of awakenings decreased by 0.60

Benzodiazepine Use Is Costly

- Retrospective study evaluated benzodiazepine use and subsequent healthcare costs in 17,558 veterans over age 59\(^9\)
- 1,352 patients receiving benzodiazepine prescriptions suffered injuries
  - 297 inpatient admissions
  - 2,977 outpatient visits
- Total direct medical costs → Over $3 million

What’s wrong with Non-BZD hypnotics?

- A 220% increase in ER visits related to use of Ambien\textsuperscript{10}
- Risk of hip fracture was increased in SNF patients taking “Z drugs” \textsuperscript{11}
- More likely to have vertebral and non-vertebral fracture than short acting BZD\textsuperscript{12}
- Reports of problem behaviors while asleep\textsuperscript{13}
  - Sleep driving, eating, making phone calls

10. Anon., A sharp rise in ED visits involving the sleep medication zolpidem. May 2013 Newswise.com
# BZD-like Drugs

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Onset (min)</th>
<th>Half Life (hrs)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>1-3mg</td>
<td>30</td>
<td>6</td>
<td>Duration 8hrs CYP 450 metabolism Onset and Maintenance</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>5-20mg</td>
<td>30</td>
<td>1</td>
<td>Duration 4hrs CYP metabolism Onset only</td>
</tr>
<tr>
<td>Zolpidem (Ambien) CR</td>
<td>5-10mg</td>
<td>30</td>
<td>1.4-4.5</td>
<td>Duration 8hrs CYP metabolism Onset only</td>
</tr>
<tr>
<td>Zolpidem (Ambien) Spray/ SL</td>
<td>6.25/12.5mg 1.75/3.5mg</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Herbal Supplements used for Insomnia

- Melatonin: Dose 1-10mg
- Chamomile: Dose varies depending on formulation
  – Maybe used for anxiety
  – Allergies
- Valerian Root: Dose varies
  – Similar in mechanism to BZD’s
Miscellaneous Agents: Rozerem (Ramelteon)

- Not addicting
- Works like Melatonin
- Dose 8 mg
- Onset of effect 30 min
- Half life 1-2.6hr/2-5hrs metabolite
- Duration of action 8hrs
Miscellaneous Agents: Trazodone

- Also used for depression
- May cause dizziness, priapism
- Dose may need to be increased to effect
- Not habit forming/No tolerance to dose
- Dose 25 - 150 mg
- Onset of effect: 30 - 60 minutes
- Duration of action 5-9hrs
Miscellaneous Agents: Remeron (Mirtazapine)

- Dose 7.5-15mg
- Onset of effect: unknown
- Half life 20-40hrs
- Increases risk of RLS
- Used for depression induced insomnia
Miscellaneous Agents: Silenor (Doxepin)

- Dose 3-6mg
- Half life 15hr/31hr for metabolite
- Duration of action 7-8hrs
- Does not improve sleep latency
- Sleep maintenance
  - Increased by 52 min in week one and 63 min by week 4
• Sedating Antihistamines: Diphenhydramine/Doxylamine
  – Dose 25-50mg
  – Onset of effect 30-60min
  – Half life 3-10 hrs
  – >10 days can lead to tolerance: “off night” every 3 days
  – Minimally effective
Orexin-receptor antagonist

- **Suvorexant (Belsomra):** 5mg 10mg 15mg 20mg
  - Blocks OX1R and OX2R inhibiting wakefulness
  - Dose: 10-20mg
  - Should be taken w/in 30 min of going to bed
  - Stay in bed for 7hrs: Long half life: 12 hrs
  - Side effects: Day time sedation, behavioral/cognitive changes/sleep paralysis
  - COPD/Sleep apnea
Case # 1

- 70yo F is here for follow up
- Hx of HTN, Anxiety, Insomnia and Chronic back pain
- Today her main complaint is insomnia. She has tried implementing some sleep hygiene tips w/o success
- Her current med list:
  - Lisinopril 20mg qday
  - HCTZ 12.5mg qday
  - Effexor XR 150 mg qday
  - Tramadol 50mg tid PRN pain
  - Ibuprofen 400mg tid
- You want to prescribe Trazodone 50mg qhs
Things to Consider

- Drug interaction risk
  - 5HT Syndrome
  - Actual vs. Theoretical
- What is the cause of insomnia?
  - Sleep hygiene issues
  - Pain: Timing of pain medications
- Other alternatives for treatment of insomnia
Case #2

- 81 yo F living alone in an upscale community in No Cal
- Husband recently died
- Family close by
- Active in the community
  - Friends
  - Bridge/book club
  - Volunteers at local hospital
- A few months ago going to her shift in the hospital in the morning trips and falls injuring her knee
- Family has noticed an overall decline
- Has been followed by the same doctor for years
## Medication list

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>DIRECTIONS</th>
<th>SPECIAL INSTRUCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone 10mg</td>
<td>1 tablet oral every 4 hours</td>
<td>For pain management</td>
</tr>
<tr>
<td>Oxycotin extended release 10mg</td>
<td>1 tablet oral every 8 hours</td>
<td>For pain management</td>
</tr>
<tr>
<td>Zegerid packet 40-1,680 mg</td>
<td>Take 1 packet mixed with 30 ml water once a day before breakfast</td>
<td>For GERD</td>
</tr>
<tr>
<td>Diovan HCT 80-12.5mg</td>
<td>1 tablet oral once a day</td>
<td>For HTN</td>
</tr>
<tr>
<td>Propranolol 80mg</td>
<td>1 tablet oral twice a day</td>
<td>For HTN</td>
</tr>
<tr>
<td>Lexapro 20mg</td>
<td>1 tablet oral once a day</td>
<td>For depression</td>
</tr>
<tr>
<td>Alvesco HFA aerosol inhaler 160mcg/actuation</td>
<td>1 puff inhalation twice a day</td>
<td>For lung disease</td>
</tr>
<tr>
<td>Docusate Sodium 250mg (OTC)</td>
<td>1 capsule oral twice a day</td>
<td>For bowel management</td>
</tr>
<tr>
<td>Oyster shell calcium with Vitamin D3 500mg-200 unit (OTC)</td>
<td>1 tablet oral three times a day</td>
<td>For supplement</td>
</tr>
<tr>
<td>Ambien 5mg</td>
<td>1 tablet oral at bedtime</td>
<td>For insomnia</td>
</tr>
</tbody>
</table>
Things to Consider

- Polypharmacy issues
- Drug cascades
- Risks associated with using Ambien
- Selecting an antidepressant for multiple purposes
Questions?