

Pharmacotherapy of Insomnia, Anxiety and Depression in Older Adults

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C³OA

*Cultivating a Culture
of Caring for Older Adults*

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

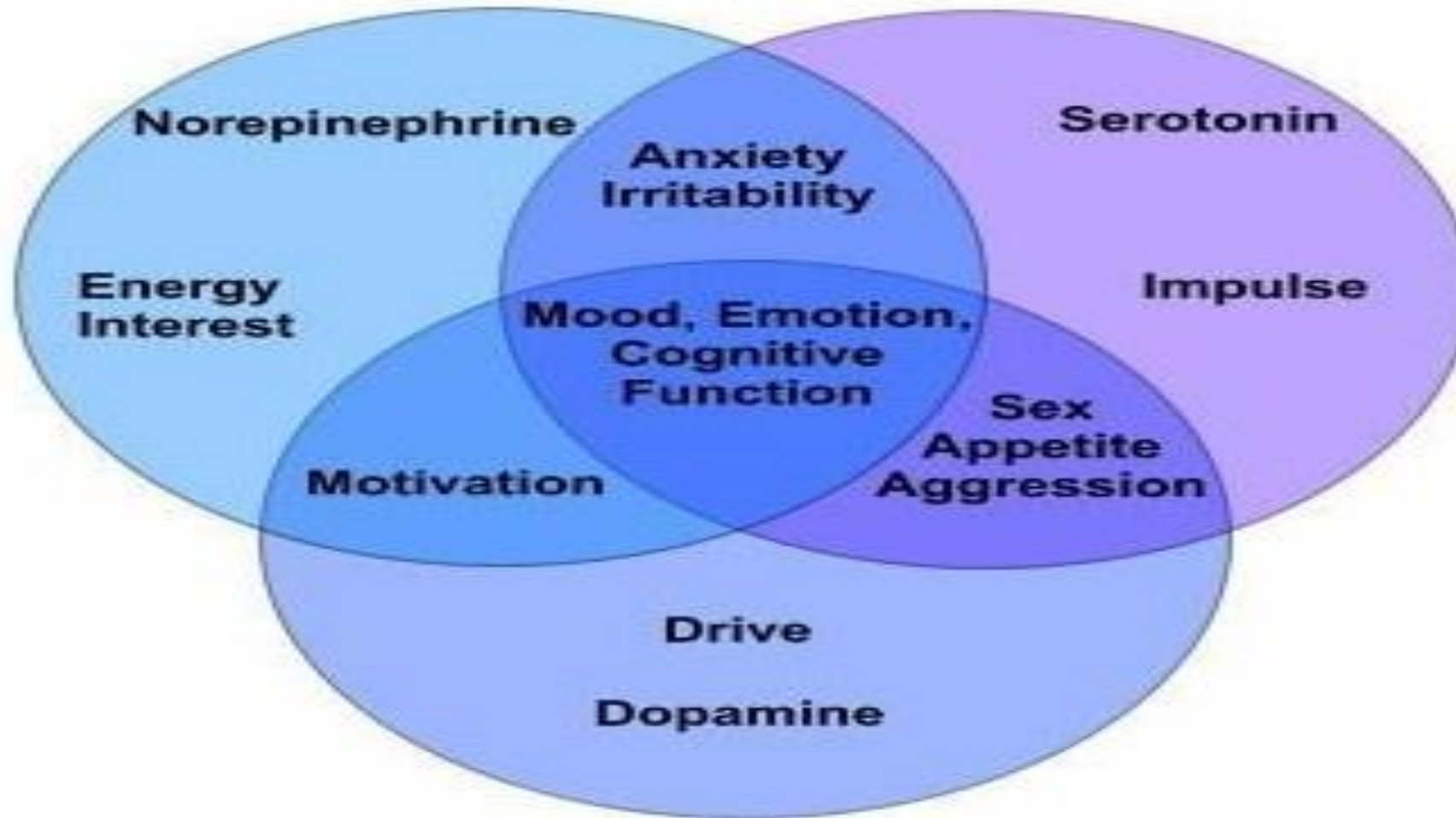
Treatment of Anxiety Disorders

- 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

Drugs	Dose (mg)	PK	Side effects	Geriatric Considerations
Clonazepam	Start with 0.25mg and titrate up slowly	T1/2 up to 40 hrs Peak Onset 1-4 h	Sedation, dizziness, mental status changes	LONG acting BZD Risk of falling, confusion
Lorazepam	Start with 0.25mg and titrate up slowly	T1/2 10-20 hr Peak Onset 1-1.5hr Not effected by age	Sedation dizziness, Mental status changes	Risk of falling, confusion
Alprazolam	Start with 0.25mg and titrate up slowly	T1/2 6-20 hrs Peak Onset 30 min-1.5hr	Sedation, dizziness mental status changes	Risk of falling confusion
Buspirone	5-60	Dosed bid or tid	GI, Dizziness, Weight changes, sexual dysfunction, bleeding	Must be dosed on a schedule. Similar to SSRI's. Takes 4-6 weeks for full effect

Neurotransmitters



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^{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 1st anti-depressant to be FDA approved for anxiety
- Treatment of anxiety takes 4-6 weeks before efficacy can be seen

Trazodone³

- 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)



Bupropion³

- 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

Mirtazapine³

- 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

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

Insomnia is Common in Seniors and has Many Consequences

- Prevalence
 - 6-18% of the general population¹
 - 57% of persons age 65+^{2,3}
- Costs
 - \$30-35 billion annually in direct & indirect costs⁴
- Consequences:
 - Daytime dysfunction, decreased quality of life, psychiatric disorders, falls, increased mortality⁵

1. Ohayon MM. Sleep Med Rev. 2002;6(2):97.

2. Foley DJ, et al. Sleep. 1995;18(6):425-432.

3. Taylor SR, Weiss JS. Popul Health Manag. 2009;12(6):317-323.

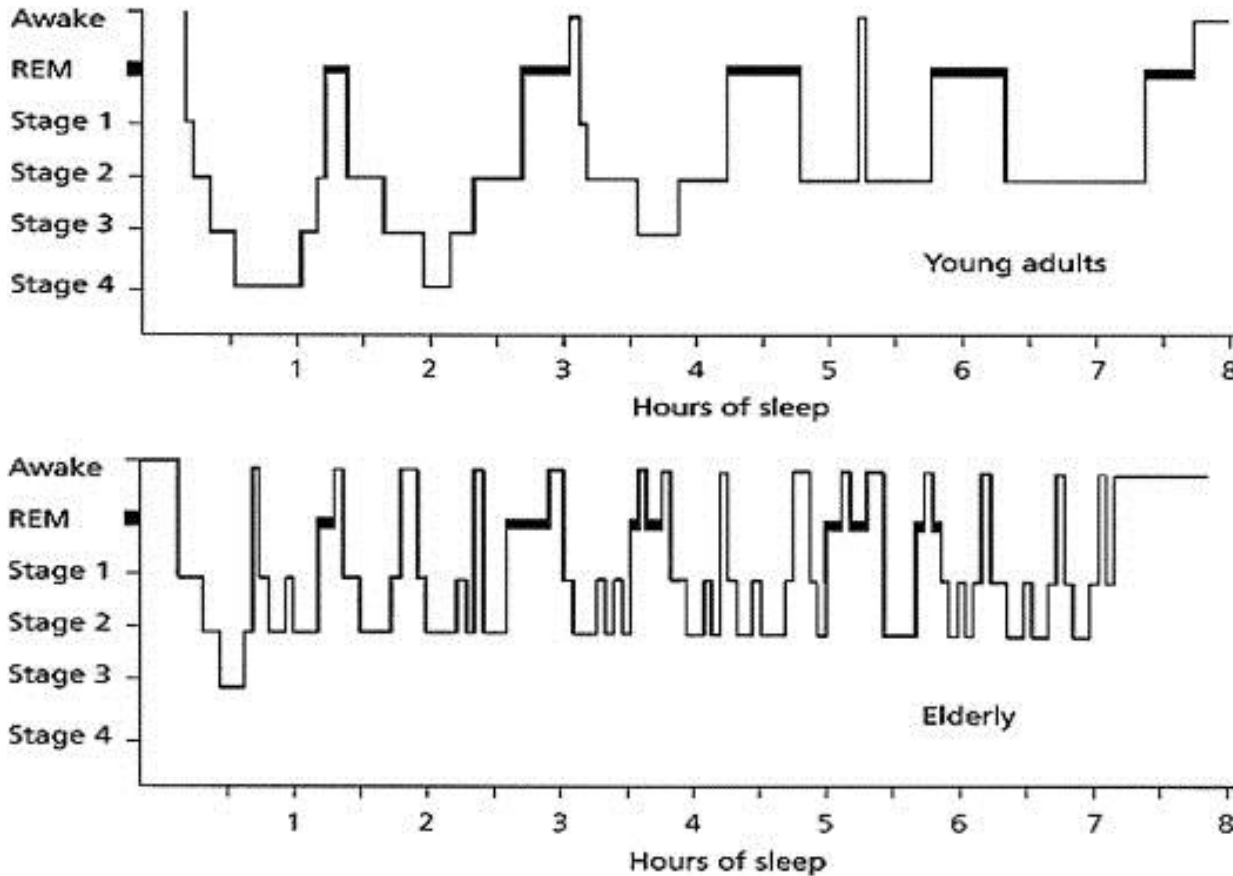
4. Chilcott LA, Shapiro CM. Pharmacoeconomics. 1996;10(Suppl 1):1-14.

5. Bain KT. Am J Geriatr Pharmacother. 2006;4(2):168-192.

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 Ageing⁶



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

6. Nabil S. Kamel, MD, Julie K. Gammack MD, Insomnia in the Elderly: Cause, Approach, and Treatment, *The American Journal of Medicine*, (2006) 119, 463-469.

What effect do Hypnotics have on Sleep Cycle?

- Shorten stage I: faster sleep onset
- Shorten Stage III and IV: Less deep restorative sleep
- Extend stage II: More time spent in less deep 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

7. Irwin MR, et al. *Health Psychol.* 2006;25(1):3-14.

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/out door 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+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

8. Glass J, et al. *BMJ*. 2005;331(7526):1169.

A Meta Analysis of Risks and Benefits of BZD's and BZD-like Drugs⁸

- 8 studies of 601 pts increase in sleep time was 25.2 min
- 8 studies of 524pts 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

8. Glass J, et al. *BMJ*. 2005;331(7526):1169.

Benzodiazepine Use Is Costly

- Retrospective study evaluated benzodiazepine use and subsequent healthcare costs in 17,558 veterans over age 59⁹
- 1,352 patients receiving benzodiazepine prescriptions suffered injuries
 - 297 inpatient admissions
 - 2,977 outpatient visits
- Total direct medical costs → Over \$3 million

9. French DD, et al. *Agency for Healthcare Research and Quality (US)*; 2005.

What's wrong with Non-BZD hypnotics?

- A 220% increase in ER visits related to use of Ambien¹⁰
- Risk of hip fracture was increased in SNF patients taking “Z drugs”¹¹
- More likely to have vertebral and non-vertebral fracture than short acting BZD¹²
- Reports of problem behaviors while asleep¹³
 - Sleep driving, eating, making phone calls

10. Anon., A sharp rise in ED visits involving the sleep medication zolpidem. May 2013 [Newswise.com](#)

11. Berry, et al, *JAMA Intern Med* 2013, 3795

12. Finkle WD, et al. *J Am Geriatr Soc.* 2011;59:1883-1890.

13. Zammit, Comparative tolerability of new agents for insomnia *Drug Saf* 2009; 32: 735-48

BZD-like Drugs

Name	Dose	Onset (min)	Half Life (hrs)	Comments
Eszopiclone (Lunesta)	1-3mg	30	6	Duration 8hrs CYP 450 metabolism Onset and Maintenance
Zaleplon (Sonata)	5-20mg	30	1	Duration 4hrs CYP metabolism Onset only
Zolpidem (Ambien) CR Spray/ SL	5-10mg 6.25/12.5mg 1.75/3.5mg	30	1.4-4.5	Duration 8hrs CYP metabolism Onset only

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

Options for Non-Geriatric Patients

- 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 over all decline
- Has been followed by the same doctor for years

Medication list

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

Things to Consider

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

Questions?

