Key Points

• Comorbid psychiatric and/or medical conditions largely responsible.
• Older adults take longer to fall asleep and have more nighttime wakefulness.
• Less slow-wave sleep in older adults.
• Treatment guided by causes.
• Cognitive-behavioral therapy is first-line treatment.
Sleepless in Iowa City

• Independently functioning 90 yo male with 6 years of difficulty getting and staying asleep.
• Tried many meds: alprazolam, temazepam and zolpidem.
• Currently on melatonin 5 mg during the night.
• PMH: a-fib, BPH, hypertension, arthritis and short term memory difficulty.
• Meds: ASA, metoprolol, memantine, omeprazole, oxybutynin, acetaminophen.
The rest of the story

• Wife placed in nursing home 14 months ago.
• Occasionally worries about finances.
• 5 times nightly nocturia.
• No breathing problems or restless legs.
• Normal physical exam except for irregularly irregular rhythm.
• GDS=2, MOCA= 26/30.
Definitions

Insomnia: difficulty in falling asleep or staying asleep, waking up too early or experiencing nonrestorative or poor quality sleep.

Chronic Insomnia: occurring for at least 3 nights a week for 1 month or more.

Primary Insomnia: chronic insomnia without specific underlying cause.
DSM-5: Insomnia Disorder

A. A predominant dissatisfaction with sleep quantity or quality with at least one of: difficulty initiating sleep, difficulty maintaining sleep, or early morning awakenings

B. Causes clinically significant distress or impairment

C. Occurs $\geq 3$ nights per week

D. Present for $\geq 3$ months

E. Occurs despite adequate opportunity for sleep

F. Not better explained by/occur exclusively during another sleep-wake disorder

G. Not attributable to the physiological effects of a substance

H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia
3 P’s of Acute Insomnia

- Predisposition
  - Anxiety, depression, etc.

- Precipitation
  - Sudden change in life

- Perpetuation
  - Poor sleep hygiene

- Ideally treat in the ACUTE phase, before the patient develops CHRONIC insomnia
Insomnia Epidemiology

• Complaints have little association with age.
• Prevalence of sleep disorders increase with age.
• More common in women than men.  
  Women to Men ratio:
  * young adults RR = 1.28
  * older adults RR = 1.73
Sleep Problems in the Elderly – Epidemiology and Impact

• Sleep complaints are common in older adults
  – 70% experience ≥1 symptom of insomnia\(^1\)
  – Most common symptom is difficulty maintaining sleep\(^1\)
  – 35% of individuals aged ≥65 years report nightly awakenings\(^2\)

• Insomnia has significant effects on daily lives of elderly
  – Impairments in problem solving and in working and episodic memory\(^3\)

• Risk factor for cognitive decline and increases risk of falls\(^4\)

Late-life Insomnia

• Chronic problem: 1/3 of older adults with insomnia report severe symptoms at 4 years.
• Those using hypnotics 1/3 still using at 4 yrs.
• Women >84 yrs. of age: 80% report sleeping difficulties. (regular ETOH, OTC sleep agents)
• Predictor of death and NH placement (men).
• Associated with worse quality of life.
Sleep Patterns and Aging

- waking up earlier
- increased sleep onset latency
- increased time spent in bed
- increased night time awakening
- increased napping
- decreased total sleep (especially deep)
Factors that Adversely Influence Sleep Quality

• Behavioral and environmental factors
• Psychosocial factors
• Psychiatric disorders
• Physical status
• Medication and drugs
Behavioral and Environmental

- Sleep hygiene
- Extreme temperature
- Noise or light
- Lack of exposure to light
- Physical inactivity
Psychosocial

- Stress
- Hyperarousal
- Social isolation
- Bereavement
- Change of residence
- Hospitalization
- Work status
Psychiatric

• Depression
• Anxiety
• Psychosis
• Delirium
• Schizophrenia
Physical Status

• CV disorders
• Pulmonary disease
• GI disorders
• GU disorders
• Neurodegenerative disorders

• Stroke and Seizures
• Chronic pain
• Thyroid disorder
• Diabetes
• Menopause
Medication and Drugs

- Alcohol
- Caffeine
- Nicotine
- CNS stimulants
- Beta blockers
- Thyroid hormone

- Ca channel blockers
- Decongestants
- Bronchodilators
- Corticosteroids
- Anticholinergics
- Antidepressants
Differential for Disordered Sleep

• Medical Conditions and their Treatments.
• Sleep-Related Breathing Disorders.
• Periodic Limb Movements / Restless Legs.
• Circadian Rhythm Sleep Disorders.
• REM Sleep Behavior Disorders.
• Changes in Sleep with Dementia.
Obstructive Sleep Apnea

• Common in older adults, prevalence varies.
• Consider in pt with treatment resistant hypertension.
• BMI and neck size less predictive in older pt.
• Many associations: B/P, stroke, dementia, MI, all-cause mortality.
• CPAP tolerated in older adults.
Restless legs syndrome

• Uncontrolled urge to move legs
• Uncomfortable sensation in legs during rest
• Periodic limb movements.
• Associated anemia, or renal or neurologic disease.
• Drugs: antiemetics, antipsychotics, SSRIs, tricyclics, diphenhydramine.
• TX: pramipexole, ropinirole, Sinemet, gabapentin
Circadian rhythm sleep disorder

- Common early bedtime and early morning awakening (morning lark//night owl).
- Sleep log to diagnosis and monitor therapy.
- Wrist actigraphy or polysomnogram if unclear diagnosis.
REM behavior disorder

• Act out dreams
• Lack of normal muscle atonia during REM sleep
• Rare
• Associated with: Dementia, Multiple system atrophy and Parkinson disease.
• Polysomnogram to confirm diagnosis.
Sleep changes with Dementia

- Lower sleep efficiency, higher percent N1 sleep.
- Circadian rhythm sleep disorders more common. (daytime sleeping, nighttime wakefulness)
- Cholinesterase inhibitors → vivid dreams
- ? Melatonin effect in Alzheimer disease
- Some benefit from bright light therapy
Evaluation of Sleep

• Screening questions: is patient satisfied with their sleep, fatigue interfering with ADLs, bed partner complaints about patient’s sleep?
• Sleep log for 1-2 weeks.
• Focused physical exam.
• Polysomnogram: ? Sleep apnea, narcolepsy, violent behaviors during sleep.
• Wrist actigraphy.
### TWO WEEK SLEEP DIARY

**INSTRUCTIONS:**
1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter “C” in the box when you have coffee, cola or tea. Put “M” when you take any medicine. Put “A” when you drink alcohol. Put “E” when you exercise.
3. Put a line (1) to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

**SAMPLE ENTRY BELOW:** On a Monday when I worked, I jogged on my lunch break at 1 PM, had a glass of wine with dinner at 6 PM, fell asleep watching TV from 7 to 8 PM, went to bed at 10:30 PM, fell asleep around Midnight, woke up and couldn’t get back to sleep at about 4 AM, went back to sleep from 5 to 7 AM, and had coffee and medicine at 7:00 in the morning.

<table>
<thead>
<tr>
<th>Today’s Date</th>
<th>Day of the week</th>
<th>Type of Day</th>
<th>Noon</th>
<th>1PM</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6PM</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11PM</th>
<th>1AM</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6AM</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>sample</td>
<td>Mon.</td>
<td>Work</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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Management of Sleep Problems

• Behavioral and Nonpharmacologic Interventions.

• Pharmacotherapy.
Behavioral Interventions

• Not to be confused with simple sleep hygiene.
• Cognitive-behavioral therapy CBT-I (stimulus control, sleep restriction, cognitive therapy)
• Exposure to bright light.
### Table 2. Components of Cognitive Behavioral Therapy for Insomnia.

<table>
<thead>
<tr>
<th>Component</th>
<th>Intended Effect</th>
<th>Specific Directions for Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep restriction</td>
<td>Increase sleep drive and stabilize circadian rhythm</td>
<td>Reduce time in bed to perceived total sleep time (not less than 5–6 hours), choose specific hours on the basis of personal preference and circadian timing, increase time in bed gradually as sleep efficiency improves</td>
</tr>
<tr>
<td>Stimulus control</td>
<td>Reduce arousal in sleep environment and promote the association of bed and sleep</td>
<td>Attempt to sleep when sleepy, get out of bed when awake and anxious at night, use the bed only for sleep or sexual activity (e.g., no watching TV in bed)</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Restructure maladaptive beliefs regarding daytime and health consequences of insomnia</td>
<td>Maintain reasonable expectations about sleep; review previous insomnia experiences, challenging perceived catastrophic consequences</td>
</tr>
<tr>
<td>Relaxation therapy</td>
<td>Reduce physical and psychological arousal in sleep environment</td>
<td>Practice progressive muscle relaxation, breathing exercises, or meditation</td>
</tr>
<tr>
<td>Sleep hygiene</td>
<td>Reduce behaviors that interfere with sleep drive or increase arousal</td>
<td>Limit caffeine and alcohol, keep bedroom dark and quiet, avoid daytime or evening napping, increase exercise (not close to bedtime), remove bedroom clock from sight</td>
</tr>
</tbody>
</table>


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Sleep restriction

• Intended Effect
  * increase sleep drive and stabilize circadian rhythm.

• Directions for Patients
  * Reduce time in bed to perceived total sleep time (= or > 5-6 hours)
  * Increase time in bed as sleep efficiency improves.
Stimulus control

• Intended effect
  * reduce arousal in sleep environment, promote association of bed and sleep

• Directions for Patients
  * sleep when sleepy, get out of bed when awake and anxious at night use bed only for sleep or sexual activity (no watching TV in bed)
Cognitive therapy

• Intended effect
  * restructure maladaptive beliefs about daytime and health consequences of insomnia.

• Directions for Patients
  * maintain reasonable expectations about sleep; review previous insomnia experiences, challenging perceived catastrophic consequences.
Relaxation therapy

• Intended effect
  * reduce physical and psychological arousal in sleep environment.

• Directions for Patients
  * practice progressive muscle relaxation, breathing exercise, or meditation.
Sleep hygiene

• Intended effect
  * reduce behaviors that interfere with sleep drive or increase arousal.

• Directions for Patients
  * limit caffeine and alcohol, keep bedroom dark and quiet, avoid napping, increase exercise, remove bedroom clock from sight.
Pharmacotherapy
Available Treatment Options

- Benzodiazepines
- Nonbenzodiazepine Benzodiazepine Receptor Agonists (Z-hypnotics)
- Melatonin Receptor Agonists
- Orexin Receptor Antagonists
- Antidepressants
- Antihistamines
- Natural Products
FDA-Approved Agents

Short-term Use

• benzodiazepines
  – estazolam
  – flurazepam
  – quazepam
  – temazepam
  – triazolam
• zolpidem (tablet, sublingual tablet, oral spray)
• zaleplon
• phenobarbital*
• chloral hydrate*†

**Not recommended**

†No longer available

Long-term Use (>3 mos)

• zolpidem (CR tablet)
• eszopiclone
• ramelteon
• low-dose doxepin
• suvorexant
<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>CNS receptor target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine(^1), doxylamine(^1*)</td>
<td>Antihistamines(^1)</td>
<td>H(_1)</td>
</tr>
<tr>
<td>Amitriptyline(^1*)</td>
<td>Tricyclic antidepressants(^1)</td>
<td>5HT, NE, H(_1); also DA, Ach</td>
</tr>
<tr>
<td>Trazodone(^1*)</td>
<td>Antidepressant chemically unrelated to tricyclics, tetracyclics, and MAOIs(^1)</td>
<td>5HT(_2); also α-adrenergic and modest H(_1) blockade; weakly blocks presynaptic α(_2)-adrenergic receptors and strongly inhibits postsynaptic α(_1) receptors</td>
</tr>
<tr>
<td>Olanzapine(^1*)</td>
<td>Atypical antipsychotic (structurally similar to the benzodiazepines)(^1)</td>
<td>5HT(_2)A antagonism, as well as activity at other 5HT receptors; antimuscarinic, antihistaminic and α(_1)-adrenergic antagonist properties</td>
</tr>
<tr>
<td>Quetiapine(^1*)</td>
<td>Atypical antipsychotic(^1)</td>
<td>5HT(_2)A antagonism; potent, reversible D(_2) receptor antagonist; H(_1) and α(_1)-adrenergic antagonist</td>
</tr>
<tr>
<td>Ramelteon(^1)</td>
<td>Melatonin receptor agonist(^1)</td>
<td>MT(_1), MT(_2)</td>
</tr>
<tr>
<td>Triazolam(^2), temazepam(^2)</td>
<td>Benzodiazepines(^2)</td>
<td>GABA(_\alpha) (nonselective)</td>
</tr>
<tr>
<td>estazolam(^2), quazepam(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>flurazepam(^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaleplon(^2), eszopiclone(^2)</td>
<td>Nonbenzodiazepine benzodiazepine receptor agonists (BzRAs)(^2)</td>
<td>GABA(_\alpha1) (preferential)</td>
</tr>
<tr>
<td>zaleplon extended-release(^2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Not FDA-approved for insomnia.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Adult Dose</th>
<th>$t_{1/2}$</th>
<th>$t_{max}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam C$^{IV1}$</td>
<td>Halcion®</td>
<td>0.25 mg</td>
<td>1.5-5.5 h</td>
<td>2 h</td>
</tr>
<tr>
<td>Temazepam C$^{IV2}$</td>
<td>Restoril®</td>
<td>7.5-30 mg</td>
<td>8.8 h</td>
<td>1.5 h</td>
</tr>
<tr>
<td>Estazolam C$^{IV3}$</td>
<td>ProSom™</td>
<td>1-2 mg</td>
<td>10-24 h</td>
<td>0.5-6 h</td>
</tr>
<tr>
<td>Flurazepam C$^{IV4}$</td>
<td>Dalmane®</td>
<td>15-30 mg</td>
<td>47-100 h including metabolites</td>
<td>0.5-1 h</td>
</tr>
<tr>
<td>Quazepam C$^{IV5}$</td>
<td>Doral®</td>
<td>7.5-15 mg</td>
<td>39-73 h including metabolites</td>
<td>~2 h</td>
</tr>
<tr>
<td><strong>Nonbenzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaleplon C$^{IV6}$</td>
<td>Sonata®</td>
<td>10 mg, 20 mg</td>
<td>~1 h</td>
<td>~1 h</td>
</tr>
<tr>
<td>Zolpidem tartrate C$^{IV7}$</td>
<td>Ambien®</td>
<td>5 mg, 10 mg</td>
<td>2.5 h, 2.9 h elderly</td>
<td>1.6 h</td>
</tr>
<tr>
<td>Eszopiclone C$^{IV8}$</td>
<td>Lunesta®</td>
<td>1 mg, 2 mg, 3 mg</td>
<td>~6 h, 9 h elderly</td>
<td>~1 h</td>
</tr>
<tr>
<td>Zolpidem tartrate C$^{IV9}$ (extended release)</td>
<td>AMBIEN CR®</td>
<td>6.25 mg, 12.5 mg</td>
<td>2.8 h,* 2.9 h elderly</td>
<td>1.5 h, 2.0 h elderly</td>
</tr>
</tbody>
</table>

*Terminal half-life. $t_{1/2}$ = elimination half-life; $t_{max}$ = time to maximal concentration.


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Benzodiazepines

- Benzodiazepines – GABA-A receptors
  - Benefits: cheap, improve sleep latency, total sleep time, number of awakenings, sleep quality
  - Disadvantages:
    - More next day effects (drowsy, dizzy)
    - More dependency/withdrawal
    - More rebound symptoms
    - More anterograde amnesia (especially with shorter acting agents)
    - Falls and hip fracture risk (long acting)

NBzRA Agents

Zolpidem (Ambien)
• Short half life (2.6 hours, 2.8 for “CR”)
• Better for sleep onset insomnia
  – Minimal impact on sleep architecture
• “CR” not directly compared with Ambien
• Can see rebound insomnia, mild next day drowsiness, mild antegrade amnesia
• “CR” approved for long term use

Zaleplon (Sonata)
• Ultrashort half-life (1 hour)
• Better for sleep onset insomnia
  – Can increase total sleep time and efficiency
• Can be taken after a middle of night awakening
• Rare rebound and next day effects
• Not approved for long term use
  – But reported to be safe for long term use in elderly

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Eszopiclone (Lunesta)

- Medium half life (5-7 hours)
- Better for sleep maintenance insomnia
  - Increased total sleep time 49 min
- Helps with sleep onset (27 min)
- Few next day effects (but longer half life suggest risk for next day effects in elderly)
- Approved for long term use
NBzRA Agents

– Advantages
  • more specific targeting of GABA receptors in the brain – so less side effects?
  • Data for efficacy up to 6-12 months (zolpidem, eszopiclone)
  • Better for sleep onset insomnia – minimal impact on sleep architecture
  • May be used for middle of night awakenings (low-dose zolpidem sublingual tablet, zaleplon)
  • Low likelihood of rebound insomnia

– Disadvantages
  • Not well studied in the elderly (use lower starting doses)
  • Not compared against each other
  • More expensive ($65-100 per month)
  • Dependence/withdrawal still occur
  • Still can increase risk of falls and fractures

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NBzRA Abuse Potential

• Literature review for cases of reported abuse or dependence with zolpidem or zopiclone through 2002
• Identified 36 cases with zolpidem, 22 with zopiclone; almost all were former drug/alcohol abusers or had another psychiatric disorder
• Because of high prescription rates for these agents, authors felt that relative risk of abuse/dependence was very low
• Conclusion: pts with Hx substance abuse and other psychiatric disorders at ↑ risk for abusing zolpidem or zopiclone
• Likely that cases of abuse/dependence are underreported in the literature
Sedative-Hypnotics Risk/Benefit

• Meta-analysis of 24 studies, > 2400 patients older than age 60 treated with benzo’s or benzo receptor agonists
  – Benefits – compared to placebo (NNT = 13)
    • Small improvement in sleep quality
    • Sleep time increased (25 minutes)
    • Decrease number of awakenings (0.63)
  – Harms (NNH = 6)
    • Cognitive impact (4.78 times more common)
    • Psychomotor events (2.61 times as common)
    • Daytime fatigue (3.82 times more common)

Melatonin Receptor Agonists

• Mechanism
  – Selectively binds melatonin MT1 and MT2 receptors in the hypothalamus, which appear to contribute to normal sleep-wake cycle

• Products
  – Ramelteon (Rozerem®) - 2005

• Pharmacokinetics
  – High-fat meals delay absorption and onset

<table>
<thead>
<tr>
<th>Medication</th>
<th>Onset (min)</th>
<th>Duration</th>
<th>Half-life (hr)</th>
<th>CYP450 Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ramelteon</td>
<td>30</td>
<td>Short</td>
<td>1-5</td>
<td>1A2</td>
</tr>
</tbody>
</table>

• Dosing
  – 8 mg administered within 30 min of bedtime
Ramelteon Considerations

Advantages
- No rebound insomnia
- Not a controlled substance
- Small improvement in sleep onset (8 min)
- Improved total sleep time (12 min)
- Increase prolactin levels, few other side effects.
- Approved for chronic use.

Disadvantages
- May be less helpful for sleep maintenance difficulties
- Not compared to other drugs or melatonin.
- Expensive
Orexin Receptor Antagonists

• Mechanism
  – Blocks binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R, which is thought to suppress wake drive

• Products
  – Suvorexant (Belsomra®) – 2014

• Pharmacokinetics
  – High-fat meals delay absorption and onset

<table>
<thead>
<tr>
<th>Medication</th>
<th>Onset (min)</th>
<th>Duration</th>
<th>Half-life (hr)</th>
<th>CYP450 Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>suvorexant</td>
<td>30</td>
<td>Intermediate</td>
<td>12</td>
<td>3A4</td>
</tr>
</tbody>
</table>

• Dosing
  – 10-20 mg administered within 30 min of bedtime
Suvorexant Considerations

Advantages

• No rebound insomnia
• No evidence of withdrawal

Disadvantages

• C-IV controlled substance
• Expensive
# Brief Overview of Evidence: Benzodiazepines, NBzRAs, Ramelteon

<table>
<thead>
<tr>
<th>Medication</th>
<th>Author, Year, Design</th>
<th>Dose</th>
<th>Treatment Duration</th>
<th>Sleep Onset Latency</th>
<th>Total Sleep Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>zolpidem &amp; benzos</td>
<td>Nowell, 1997, Meta-analysis</td>
<td>zolpidem: 10-15 mg*</td>
<td>Up to 5 wks</td>
<td>-5.95 min</td>
<td>+5.64 min</td>
</tr>
<tr>
<td>zaleplon</td>
<td>Barbera, 2005, Review</td>
<td>10 mg</td>
<td>4-5 wks</td>
<td>-7.9 min</td>
<td>Not significant</td>
</tr>
<tr>
<td>eszopiclone</td>
<td>Najib, 2006, Review</td>
<td>2-3 mg</td>
<td>Up to 4 wks</td>
<td>-10 min (2 mg)</td>
<td>+22.1 min (2 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-11.5 min (3 mg)</td>
<td>+31.3 min (3 mg)</td>
</tr>
<tr>
<td>ramelteon</td>
<td>Roth, 2006, RCT</td>
<td>4-8 mg</td>
<td>5 wks</td>
<td>-7.2 min (4 mg)</td>
<td>Not significant</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-12.9 min (8 mg)</td>
<td></td>
</tr>
<tr>
<td>suvorexant</td>
<td>Herring, 2012, RCT</td>
<td>10-80 mg</td>
<td>4 wks</td>
<td>-2.3 min (10 mg)</td>
<td>+22.3 min (10 mg)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-22.3 min (20 mg)</td>
<td>+49.9 min (20 mg)</td>
</tr>
</tbody>
</table>

*Included studies with estazolam, flurazepam, lorazepam, triazolam, temazepam, & quazepam at varying doses

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Best Agents for Specific Complaints

• Sleep onset difficulties
  – Rapid onset with short half-life
    • zaleplon, ramelteon, triazolam (not first line)

• Sleep onset and maintenance difficulties
  – Rapid onset and longer half-life
    • zolpidem, eszopiclone, suvorexant

• Sleep maintenance difficulties
  – Delayed onset with long half-life
    • temazepam, estazolam
Antidepressants

• Mechanisms for insomnia
  – $H_1$, $5HT_{2A}$, and muscarinic AChR antagonism

• Commonly used products
  – trazodone (Desyrel®) - 1981
  – amitriptyline (Elavil®) - 1961
  – doxepin (Sinequan®) - 1969
    • low-dose tablets (Silenor®) - 2010
  – mirtazapine (Remeron®) - 1996

• Dosing: generally lower than antidepressant doses
Antidepressant Adverse Effects

- Trazodone: dizziness, sedation, dry mouth, hypotension, headache, hangover effect, priapism (rare)
- Amitriptyline/doxepin: sedation, anticholinergic effects, cardiac arrhythmias
- Mirtazapine: sedation, increased appetite, weight gain, dry mouth
Antidepressant Considerations

Advantages

• Not controlled substances
• Best used in patients with comorbid depression
• Relatively low cost

Disadvantages

• Limited data
• TCAs: increased risk of confusion and anticholinergic effects in elderly
Evidence for Trazodone in Insomnia

• Literature review 1980-2003
• 18 studies identified
  – only 5 with N > 30; only 3 randomized, double-blind, placebo-controlled
• 14 of 18 studies enrolled pts with depression or dysthymia
  – High variability in methodology
  – Improvements in subjective assessments of sleep and objective measures of total sleep time and # nighttime awakenings; suggestion of hangover effect

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Trazodone vs. zolpidem

- 306 non-depressed adult pts with DSM-III-defined primary insomnia
- Randomized 1:1:1 to trazodone 50 mg HS, zolpidem 10 mg HS, or placebo for 14 days (double-blinded, 10 U.S. sites)
- Primary outcomes: pt-reported sleep latency & duration
- Results
  - Week 1: trazodone & zolpidem superior to placebo for sleep latency & duration, zolpidem superior to trazodone for latency
  - Week 2: only zolpidem superior to placebo for latency, no differences from placebo in duration
- Limitations: doses not necessarily equivalent, short duration, no objective measures, excluded pts with substance use disorders

Walsh et al. *Hum Psychopharm* 1998
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Antihistamines

• Mechanisms for insomnia
  – $H_1$ and muscarinic AChR antagonism

• Commonly used products
  – diphenhydramine
  – doxylamine

• Dosing
  – 25-50 mg diphenhydramine or doxylamine

• Adverse Effects
  – Dizziness, dry mouth, constipation, morning sedation; anticholinergic activity (elderly)

• BEERs list drugs
Evidence for Melatonin in Insomnia

• Meta-analysis of 17 randomized, double-blind, placebo-controlled trials (N=284 subjects)
  – Melatonin dose range 0.1 - 80 mg (mean 7.4 mg, median 2 mg)
  – Large study heterogeneity; duration up to 4 wks
  – Sleep efficiency improved by 2.2% (95% CI: 0.2 - 4.2) and total sleep duration ↑ by 12.8 minutes (95% CI: 2.9 - 22.8) across studies

• Randomized, double-blind, placebo controlled trial of 334 pts aged 55-80 yrs
  – Melatonin 2 mg prolonged-release vs. placebo
  – 26% pts on melatonin had improvement on self-reported measures of sleep quality and behavior following wakefulness at 3 weeks vs. 15% on placebo [p=0.011, OR: 1.97 (95% CI: 1.14-3.41)]
  – Mean baseline-adjusted sleep latency time improved by 8.8 minutes (p=0.028) compared to placebo
Recommendations for Sleepless in Iowa City

• Continue good sleep hygiene.
• Set expectations.
• Start tamsulosin at bedtime.
• Take melatonin 5 mg, ½ hour before bedtime.
• Discontinue memantine.
• If sleep not improve consider trazodone 25-50 mg qhs.
Summary

• Encourage good sleep hygiene
• Recognize 3 P’s of acute insomnia (predisposition, precipitation, perpetuation)
• Treat comorbidities
• Low threshold for trazodone or melatonin
• Rx: Hypnotics...with a plan