Managing Insomnia in the Real World
ARS PRE QUESTIONS
Managing Insomnia in the Real World
Prevalence of Insomnia
Second highest health-related complaint world-wide

2% Every Night
19% A Few Nights per Week
25% A Few Nights per Month
33% Rarely

Case

- 61 y.o. c/o unrefreshing sleep following retirement, 4 months ago
- 4-5 nights per week
- Mind “spins” at bedtime
- Washed out, low energy all day, moody, irritable
- No medical contributors
- MSE psychomotor slowing; mood “fine.” Affect restricted, no h/s ideation, sensorium clear. Cognitive functions intact
What additional criterion must be met to satisfy criteria for DSM-5 insomnia disorder?

A. Duration of insomnia of at least 6 months
B. Has difficulty with insomnia on a nightly basis
C. Sleep laboratory confirmation of a sleep latency (time to fall asleep) of more than 1 hour
D. Does not suffer from major depressive disorder
E. Already meets diagnostic criteria for insomnia disorder
Insomnia Disorder

A. Dissatisfaction with sleep quantity or quality with one or more of the following:
   1. Difficulty initiating sleep (children: w/o caregiver intervention)
   2. Difficulty maintaining sleep (children: w/o caregiver intervention)
   3. Early morning awakening w/inability to return to sleep

B. Significant distress or impairment

C. > Three nights per week

D. > Three months

E. Adequate opportunity for sleep

Specify if:
   - With non–sleep disorder mental comorbidity
   - With other medical comorbidity
   - With other sleep disorder

Criteria F, G, and H not shown; not all specifiers shown
DSM-5, American Psychiatric Association, 2013
Impairments Associated with Insomnia

- Diminished ability to enjoy family and social relationships
- Decreased quality of life
- Increased absenteeism and poor job performance
- Motor vehicle crashes
- Increased risk of falls
- Impaired concentration and memory
- Increased incidence of pain
- Enhanced risk of present and future psychiatric disorders
- Hypertension
- Diabetes
- Increased mortality

Ancoli-Israel S et al. (1999), Sleep 22(suppl 2):S347-S353
Which of the following would be the most appropriate next step?

A. Exploration of behaviors just prior to bedtime and during the day
B. Asking about a family history of insomnia
C. A referral for neuropsychological testing
D. Treatment with an antidepressant
E. Short course of treatment with a hypnotic medication
The Do's of Sleep Hygiene

- Awaken at the same time every morning
- Increase exposure to bright light during the day
- Establish a daily activity routine
- Exercise regularly in the morning and/or afternoon
- Set aside a worry time
- Establish a comfortable sleep environment
- Do something relaxing prior to bedtime
- Try a warm bath

The Don'ts of Sleep Hygiene

Avoid…

- Alcohol
- Caffeine, nicotine, and other stimulants
- Exposure to bright light during the night
- Exercise within 3 hours of bedtime
- Heavy meals or drinking within 3 hours of bedtime
- Using your bed for things other than sleep (or sex)
- Napping, unless a shift worker
- Watching the clock
- Trying to sleep
- Noise
- Excessive heat/cold in room

Evaluation and Management of Insomnia

- **Sleep history**
  - Symptoms, duration, frequency, course, precipitants, treatments, responses
  - Sleep/wake schedule (sleep logs)
  - Bedtime and daytime activities
  - Extent of daytime impairment (Epworth Sleepiness Scale)
  - Severity (Insomnia Severity Index)

- **Identify and treat comorbid conditions**

- **Address insomnia directly**
  - Effective for a broad range of patients
  - Includes behavioral therapy and hypnotic medications
Increased Prevalence of Medical Disorders in Individuals With Insomnia

Community-based population of 772 adults
Case: Mary

- 88 y.o married woman complains of insomnia (initiation and maintenance) for 6 months, after an auto accident followed by brief LOC and full recovery
- Tried diphenhydramine, DC’d due to side effects
- Bed 10 pm to 5 am, sleep latency 1-2 hours, 10 brief awakenings, fatigued all day yet resists napping
- No snoring, no limb movements, tosses and turns all night
- Cardiomyopathy (recent EF 35%), mitral valve disease, osteoporosis, HTN, glaucoma, all stable
- Meds: Ramipril, latanosport
- Exam: BMI 23, normal vital signs, PE, and MSE
Which of the following would be the most appropriate next step?

A. Brain MRI
B. Polysomnography
C. Cognitive behavioral therapy
D. Melatonin 1-3 mg at bedtime
E. Zolpidem extended release 6.25 mg at bedtime
Sleep Disordered Breathing and Heart Failure

• Sleep disordered breathing is present in 76% of heart failure patients
  – 40% central (CSA)
  – 36% obstructive sleep apnea (OSA)
  – Despite optimal medication (ACE-i, AT-1-bl, diuretics, β-blockers, spironolactone and dig)
• Preferred treatment options are positive airway pressure devices and nocturnal oxygen
• Hypnotics (zolpidem and triazolam) raise the risk of respiratory suppression in the setting of primary CSA
  – May improve sleep quality
  – Modest negative effects on oxygen saturation
  – Last therapeutic option

Aurora RN et al. SLEEP 2012;35(1):17-40
Selected Comorbid Conditions and Treatment Examples

- Obstructive sleep apnea
  - CPAP, BIPAP, oral appliances, upper airway surgery
- Restless legs syndrome
  - Alpha 2 delta ligands, dopaminergic agents
- Major depressive disorder
  - Antidepressants
- GERD
  - Proton pump inhibitors, H-2 receptor blocker
- Shift work disorder
  - Bedtime melatonin, modafinil/armodafinil prior to shift, bright light therapy
- Medication-induced insomnia
  - Dosage or medication change

Doghramji K et al. *Focus VII* (4): 441-454, 2009
# Psychological and Behavioral Treatments for Primary Insomnia

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus control therapy*</td>
<td>If unable to fall asleep within 20 minutes, get OOB and repeat as necessary</td>
</tr>
<tr>
<td>Relaxation therapies*</td>
<td>Biofeedback, progressive muscle relaxation</td>
</tr>
<tr>
<td>Restriction of time in bed</td>
<td>Decrease time in bed to equal time actually asleep and increase as sleep efficiency improves</td>
</tr>
<tr>
<td>(sleep restriction)</td>
<td></td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Talk therapy to dispel unrealistic and exaggerated notions about sleep</td>
</tr>
<tr>
<td>Paradoxic intention</td>
<td>Try to stay awake</td>
</tr>
<tr>
<td>Sleep hygiene education</td>
<td>Promote habits that help sleep; eliminate habits that interfere with sleep</td>
</tr>
<tr>
<td>Cognitive-Behavioral Therapy*</td>
<td>Combines sleep restriction, stimulus control and sleep hygiene education with cognitive therapy</td>
</tr>
</tbody>
</table>

*Standard Treatment according to American Academy of Sleep Medicine
Morgenthaler T et al. *Sleep*. 2006;29:1415
Internet-Based CBT for Insomnia

http://www.shuti.net/
http://cbtforinsomnia.com/
Nonprescription Agents for Insomnia: Limited Evidence for Hypnotic Efficacy

<table>
<thead>
<tr>
<th>Product</th>
<th>Latin name (or generic name)</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valerian root</td>
<td><em>V. officinalis L.</em></td>
<td>Restless sleep, gastrointestinal upset, headache, contact allergies, mydriasis, possible carcinogen, possible hepatotoxicity</td>
</tr>
<tr>
<td>First-generation histamine-1-receptor antagonists</td>
<td>Diphenhydramine hydrochloride, diphenhydramine citrate, doxylamine succinate</td>
<td>Vomiting, depression, malaise, drowsiness, impaired mentation, extrapyramidal reactions, rhabdomyolysis, dry mouth, weakness, gastrointestinal upset, headache, impotence, urinary retention, increased intraocular pressure</td>
</tr>
</tbody>
</table>
Nonprescription Agents for Insomnia: Insufficient Evidence for Hypnotic Efficacy

<table>
<thead>
<tr>
<th>Product</th>
<th>Latin name</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hops</td>
<td><em>Humulus lupulus</em></td>
<td>Unknown, vomiting, allergic reactions</td>
</tr>
<tr>
<td>Chamomile</td>
<td><em>Matricaria recutita</em></td>
<td>Unknown</td>
</tr>
<tr>
<td>Lemon balm</td>
<td><em>Melissa officinalis</em></td>
<td>Fatigue, gastrointestinal upset, dizziness, anxiety, headache, photosensitivity, phototoxicity</td>
</tr>
<tr>
<td>St. John's wort</td>
<td><em>Hypericum perforatum</em></td>
<td></td>
</tr>
<tr>
<td>Patrinia root</td>
<td><em>Patrinia Scabiosaefolia Fisch</em></td>
<td>Nausea</td>
</tr>
<tr>
<td>Niacin</td>
<td>Niacin, niacinamide, vitamin B&lt;sub&gt;3&lt;/sub&gt;</td>
<td>None known at recommended daily allowances</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium</td>
<td>None known at recommended daily allowances</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;, cyanocobalamin, hydroxocobalamin, methylcobalamin</td>
<td>None known at recommended daily allowances</td>
</tr>
<tr>
<td>Dietary changes</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Yoku-kan-san-ka chimpi-hange</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Melatonin Meta Analysis in Primary Sleep Disorders

• 19 placebo-controlled studies, 1683 subjects. Melatonin demonstrated efficacy in
  – Reducing sleep latency (WMD= 7.06 minutes)
  – Increasing total sleep time (WMD = 8.25 minutes
    • Effects magnified with longer duration and higher doses
  – Improved sleep quality (standardized mean difference = 0.22)
    • No significant effects of trial duration and melatonin dose

Melatonin Impairs Glucose Tolerance

Comparison between the effects of placebo and melatonin administrations on plasma glucose and insulin concentrations in response to an oral load of glucose (75 g) performed in the morning (09:00) and evening (21:00). TF, time fasting; T30, 60, 90, 120, and 180, time after OGTT (min); AUC120, paired t-test for AUC (melatonin and placebo) calculated with 120 min; ANOVARm, two-way ANOVA for time and treatment effects with repeated measurements. When ANOVA was significant, paired t-test was used to evaluate times in which variations were different. * Different from placebo at that time, P < 0.05. Rubio-Sastre P, et al. SLEEP 2014;37(10):1715-1719
Prescription Agents for Insomnia

- FDA-non-approved for insomnia
  - Sedating antidepressants
  - Antipsychotics like quetiapine
  - Anticonvulsants
- FDA-approved hypnotics
  - Benzodiazepine receptor agonists (BzRA’s)
    - Benzodiazepines
    - Nonbenzodiazepines
  - Melatonin receptor agonist
  - H-1 receptor antagonist
  - Orexin receptor antagonist

Insomnia and Hyperarousal

Hyperarousal

- HPA axis activation
- Increased body metabolic rate
- Cognitive arousal
- EEG arousal
- Heightened brain metabolism
- Sympathetic activation
Hypocretins and The Sleep Arousal Switch

Waking: Balance is shifted towards greater activity in wake promoting systems.

Sleep: Balance is shifted towards greater activity in sleep promoting systems.

### Benzodiazepine Receptor Agonists: The Benzodiazepines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Range(^\d) (mg)</th>
<th>Onset of Action</th>
<th>Half-life (h)</th>
<th>Short-term Limitation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estazolam</td>
<td>0.5 – 2</td>
<td>Rapid</td>
<td>10 - 24</td>
<td>Yes</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15 – 30</td>
<td>Rapid</td>
<td>47 - 100</td>
<td>Yes</td>
</tr>
<tr>
<td>Quazepam</td>
<td>7.5 – 15</td>
<td>Rapid</td>
<td>39 - 100</td>
<td>Yes</td>
</tr>
<tr>
<td>Temazepam</td>
<td>7.5 – 15</td>
<td>Slow-Intermediate</td>
<td>9.5 -12.4</td>
<td>Yes</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.25 – 0.50</td>
<td>Rapid</td>
<td>1.5 - 5.5</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\(^\d\)Normal adult dose. Dosage may require individualization

MICROMEDEX. [http://www.micromedex.com](http://www.micromedex.com)
PDR. [www.PDR.net](http://www.PDR.net)
# Selective Benzodiazapine Receptor Agonists

<table>
<thead>
<tr>
<th></th>
<th>Zaleplon</th>
<th>Zolpidem</th>
<th>Zolpidem ER</th>
<th>Eszopiclone ER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (hours)</strong></td>
<td>1</td>
<td>1.6</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Half-life [elderly]</strong> (hrs.)</td>
<td>1</td>
<td>2.5 [2.9]</td>
<td>2.8 [2.9]</td>
<td>6 [9]</td>
</tr>
<tr>
<td><strong>Sleep latency</strong></td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Wake After Sleep Onset</strong></td>
<td>--</td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Total sleep time</strong></td>
<td>↑ (20 mg)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

Physicians Desk Reference
# Zolpidem Variants

<table>
<thead>
<tr>
<th></th>
<th>Zolpidem</th>
<th>Zolpidem</th>
<th>Zolpidem</th>
<th>Zolpidem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SL</td>
<td>Oral Spray</td>
<td>SL</td>
<td></td>
</tr>
<tr>
<td>[elderly]</td>
<td></td>
<td></td>
<td></td>
<td>Women: 1.75</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hours)</td>
<td>1.6</td>
<td>1.4</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Half-life [elderly] (hrs.)</td>
<td>2.5 [2.9]</td>
<td>2.9</td>
<td>2.7</td>
<td>2.5</td>
</tr>
</tbody>
</table>

MOTN, 4 hours remaining until AM awakening

Physicians Desk Reference
# Newer Hypnotics

<table>
<thead>
<tr>
<th></th>
<th>Ramelteon</th>
<th>Doxepin</th>
<th>Suvorexant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Melatonin agonist</td>
<td>H1 antagonist</td>
<td>Orexin antagonist</td>
</tr>
<tr>
<td><strong>Dose – mg [elderly]</strong></td>
<td>8</td>
<td>3,6 [3]</td>
<td>10-20</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (hours)</strong></td>
<td>0.75</td>
<td>3.5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Half-life [elderly] (hrs.)</strong></td>
<td>1-2.6</td>
<td>15.3</td>
<td>12</td>
</tr>
<tr>
<td><strong>Sleep latency</strong></td>
<td>↓</td>
<td>--</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Wake After Sleep Onset</strong></td>
<td>--</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Total sleep time</strong></td>
<td>--</td>
<td>--</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>None</td>
<td>None</td>
<td>IV</td>
</tr>
</tbody>
</table>

*Physicians Desk Reference*
## Phase III Studies with Suvorexant

<table>
<thead>
<tr>
<th>Reference</th>
<th>Dose (mg)</th>
<th>sTSO Month 1</th>
<th>sTSO Month 3</th>
<th>sWASO Month 1</th>
<th>sWASO Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (trial 1)</td>
<td>15, 20</td>
<td>-5.4</td>
<td>-5.2</td>
<td>-5.4</td>
<td>-2.4</td>
</tr>
<tr>
<td>1 (trial 1)</td>
<td>30, 40</td>
<td>-7.4</td>
<td>-8.4</td>
<td>-9.5</td>
<td>-6.9</td>
</tr>
<tr>
<td>1 (trial 2)</td>
<td>15, 20</td>
<td>-6.9</td>
<td>-7.6</td>
<td>-8.4</td>
<td>-7.7</td>
</tr>
<tr>
<td>1 (trial 2)</td>
<td>30, 40</td>
<td>-12.8</td>
<td>-13.2</td>
<td>-8.7</td>
<td>-8.9</td>
</tr>
<tr>
<td>2</td>
<td>30, 40</td>
<td>-12.3</td>
<td>-9.7 (12 mos)</td>
<td>-9.0</td>
<td>-9.7 (12 mos)</td>
</tr>
</tbody>
</table>

Suvorexant 30 and 40 mg doses are not approved by the FDA
sTSO: Subjective time to sleep onset; sWASO: Subjective wake after sleep onset
sTST and sWASO changes in minutes
Changes from baseline, all comparisons statistically significant relative to placebo
Selected Considerations in Choosing a Hypnotic Agent

- Initiation or maintenance insomnia
  - Initiation: Zaleplon, zolpidem, ramelteon
  - Maintenance: Doxepin low dose, zolpidem SL MOTN
  - Initiation and maintenance: Zolpidem ER, eszopiclone, suvorexant

- Respiratory compromise; safety in mild to moderate OSA/COPD
  - Ramelteon, suvorexant

- Abuse potential
  - Lowest: Ramelteon, doxepin

- Prior failure of selected medication
- Patient preference

Physicians Desk Reference
Adverse Effects of Hypnotics

• Benzodiazepine receptor agonists
  – Daytime sedation, psychomotor and cognitive impairment (depending on dose and half-life)
  – Rebound insomnia
  – Respiratory depression in vulnerable populations

• Melatonin receptor agonist
  – Headache, somnolence, fatigue, dizziness
  – Not recommended for use with fluvoxamine due to CYP 1A2 interaction

• H1 receptor antagonist
  – Somnolence/sedation
  – Nausea
  – Upper respiratory tract infection

• Orexin receptor antagonist
  – Somnolence
  – Risk of impaired alertness and motor coordination, including impaired driving; increases with dose
  – Contraindicated in narcolepsy

MICROMEDEX. Available at: www.micromedex.com; Package inserts for various compounds.
Psychiatric Disorders Comorbid with Insomnia

Point Prevalence

- Drug abuse: 4.2%
- Other psychiatric disorders: 5.1%
- Alcohol abuse: 7.0%
- Dysthymia: 8.6%
- Major depression: 14.0%
- Anxiety disorder: 23.9%
- No psychiatric disorder: 59.5%

N=580.
Case: John

- 50 year old Chemical Engineer
- Recent onset MDE, underwent remission following 12-week course of vilazodone 40 mg plus psychotherapy
- Complains of persistent initiation and maintenance insomnia, whose onset was 3+ years ago
- Lethargic all day, poor concentration, difficulty functioning
- Hypothyroidism, TSH 4.0 uU/ml (WNL) on synthroid 100 mcg
- Normal labs
Residual Symptoms Following Acute MDD Remission

N=108; 215 MDD patients received a fixed dose of fluoxetine 20 mg for 8 weeks. Presence of residual symptoms not predicted by baseline demographic characteristics or Axis I and Axis II comorbid conditions. Nierenberg et al. J Clin Psychiatry 1999;60:221-225
Complex Relationship Between Insomnia and Mood Disorders

- **Insomnia**
  - Is a common complaint in MDD
  - Is more likely to emerge prior to, than during or after, MDD first episode or recurrence
  - Is associated with higher rates of lifetime and current MDD and suicide
  - Its presence and persistence predict future MDD
  - Predicts poorer outcome in MDD (persistence, chronicity, suicidality)
  - Predicts the onset of mania in bipolar depression

Low Dose Sedating Antidepressants for Insomnia

• Trazodone, doxepin, mirtazapine, paroxetine

• Advantages
  – Sedating side effects
  – Low abuse risk
  – Large dose range

• Disadvantages
  – Efficacy not well established for insomnia
  – Side effects include daytime sedation, anticholinergic effects, weight gain, drug-drug interactions

These agents are not FDA approved for insomnia
Low Dose Atypical Antipsychotics for Insomnia

• Quetiapine, olanzapine

• Advantages
  – At appropriate doses, effective for psychotic disorders
  – Low abuse potential
  – Sedation

• Disadvantages
  – Not well investigated in insomnia disorder
  – Daytime sedation, anticholinergic effects, weight gain
  – Risk of extrapyramidal symptoms, possible TD
  – Glucose and lipid abnormalities

These agents are not FDA approved for insomnia
RCT's of Hypnotic Agents in Conjunction with SSRI in MDD

- Zolpidem 10 mg vs PBO for persistent insomnia following SSRI (fluoxetine, sertraline, paroxetine) Rx for MDD or dysthymia
  - Improvement in subjective sleep measures

- Zolpidem ER 12.5 mg plus escitalopram vs PBO plus escitalopram in MDD patients with insomnia
  - Improvement in subjective sleep measures
  - Improvement in next day functioning

- Eszopiclone 3 mg plus fluoxetine vs PBO plus fluoxetine in MDD patients with insomnia
  - Improved subjective sleep measures
  - Improved quality of life
  - Higher overall MDD remission rates

- Suvorexant 10-20 mg vs PBO for persistent insomnia following stable antidepressant management for MDD
  - Study in progress at 3 sites

Hypnotics are not FDA indicated for treatment of MDD
Asnis GM et al. (1999), J Clin Psychiatry 60(10):668-676
Conclusions

- Insomnia is a prevalent condition
- It is associated with psychological, cognitive, and systemic impairments
- Its evaluation requires a systematic history, examination, and appropriate tests
- Whenever possible, treat the comorbid disorder
- Insomnia can be directly managed by cognitive behavioral therapy, pharmacological agents, and combined strategies
ARS POST QUESTIONS
Q&A