Managing Sleep Disorders in Psychiatric Patients
ARS PRE QUESTIONS
Arousal and Sleep-Promoting Systems

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
DSM-5 Sleep Wake Disorders

- Insomnia disorder
- Hypersomnolence disorder
- Narcolepsy
- Obstructive sleep apnea hypopnea
- Central sleep apnea
- Sleep related hypoventilation
- Circadian rhythm sleep-wake disorders
- Non-rapid eye movement sleep arousal disorders
- Nightmare disorder
- REM sleep behavior disorder
- Restless legs syndrome
- Substance/medication-induced sleep 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
Insomnia and Hyperarousal

- HPA axis activation
- Sympathetic activation
- Heightened brain metabolism
- Increased body metabolic rate
- Cognitive arousal
- EEG arousal

Hyperarousal
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
Comorbid Psychiatric Disorders
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.
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

The Role of Polysomnography in the Management of Psychiatric Patients with Insomnia

• The American Academy of Sleep Medicine has stated that there is no role for PSG in the routine management of insomnia, but that PSG can be justified if there are specific reasons to suspect a primary sleep disorder, or if the insomnia does not respond to routine care.

• Unsuspected primary sleep disorders occur in about 16% of adults with depressive disorders.

Treatment Approaches for Insomnia

• Address comorbid problems.
• Examples:
  – Antidepressants for major depression
  – Proton pump inhibitors for GERD
  – Mood stabilizers for mania
  – Medication change for iatrogenic insomnia
• Address insomnia directly
  – Effective for a broad range of patients
  – Includes behavioral therapy and hypnotic medications
• Above two approaches may be combined
Depressed Insomniacs Who Receive a Hypnotic in Conjunction with Their SSRI Have Better Acute Outcomes

- Better quality of life and higher overall response rates (eszopiclone)
- Higher overall remission rates
- Superior self-reported sleep

## 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 (sleep restriction)</td>
<td>Decrease time in bed to equal time actually asleep and increase as sleep efficiency improves</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
## 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
PDR. www.PDR.net
# Selective Benzodiazapine Receptor Agonists

<table>
<thead>
<tr>
<th></th>
<th>Zaleplon</th>
<th>Zolpidem</th>
<th>Zolpidem ER</th>
<th>Eszopiclone</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] (hrs.)</strong></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>↑</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>

# Zolpidem Variants

<table>
<thead>
<tr>
<th></th>
<th>Zolpidem</th>
<th>Zolpidem SL</th>
<th>Zolpidem Oral Spray</th>
<th>Zolpidem SL</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Women: 1.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[1.75]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MOTN, 4 hours remaining until AM awakening</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (hours)</strong></td>
<td>1.6</td>
<td>1.4</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Half-life [elderly] (hrs.)</strong></td>
<td>2.5 [2.9]</td>
<td>2.9</td>
<td>2.7</td>
<td>2.5</td>
</tr>
</tbody>
</table>

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# Newer Hypnotics

<table>
<thead>
<tr>
<th></th>
<th>Ramelteon</th>
<th>Doxepin</th>
<th>Suvorexant</th>
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</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>5-20</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>

Ramelteon, Doxepin, Suvorexant, Belsomra package inserts, accessed 8/13/14
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
Restless Legs Syndrome

- Urange to move the legs, usually associated with unpleasant leg sensations
- Rest induces symptoms
- Getting active (physically and mentally) brings relief
- Evening and night make symptoms worse

### Medications that Cause/Exacerbate Symptoms

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>• Tricyclic antidepressants, amitriptyline</td>
</tr>
<tr>
<td></td>
<td>• Lithium</td>
</tr>
<tr>
<td></td>
<td>• Mianserin, mirtazapine, SSRIs</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>• Metoclopramide, prochlorperazine</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>• Sedative antihistamines</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>• Older neuroleptics (eg, haloperidol, perphenazine, levomepromazine)</td>
</tr>
<tr>
<td></td>
<td>• Quetiapine, olanzapine, risperidone</td>
</tr>
<tr>
<td>Ca(^{2+})-blockers</td>
<td>• Diltiazem, nifedipine, verapamil</td>
</tr>
<tr>
<td></td>
<td>• Phenytoin</td>
</tr>
<tr>
<td>H(_2)-blockers</td>
<td>• Cimetidine</td>
</tr>
</tbody>
</table>

Restless Legs Syndrome and Depression

• Depression and RLS are frequently comorbid
  – 2- to 4-fold risk of a depressive disorder in patients with RLS
• Dysregulation of CNS dopaminergic metabolism is potential pathophysiology to explain common co-occurrence
• Many antidepressants promote or exacerbate RLS symptoms

Iron Therapy

• If serum ferritin levels are below 50 mcg/L
  – Oral ferrous sulfate or gluconate 325 mg*
  – With Vitamin C 100-200 mg; enhances absorption*
  – Consider IV Fe if oral ineffective

• Monitor Fe levels at baseline and over time
  – Check ferritin and transferrin saturation q 3 months
  – Discontinue Fe these reach 50mcg/L or 50%, respectively

• Watch for GI irritation and constipation

Not FDA indicated for use in RLS.
## Dopaminergic Agents

| Pramipexole | • FDA approved for the treatment of moderate to severe primary RLS  
| • Dosing: 0.125-mg tablets increased as needed to 0.5 mg 2-3 hours before bedtime  
| • Adverse events*: fatigue, headache, nausea, somnolence |
| Ropinirole | • FDA approved for the treatment of moderate to severe primary RLS  
| • Dosing: 0.25-mg tablets increased as needed to 4 mg 1-3 hours before bedtime  
| • Adverse events*: dizziness, nausea, somnolence, vomiting |
| Rotigotine | • FDA approved for the treatment of moderate to severe primary RLS  
| • Dosing: 1 mg/24 hours (transdermal patch) increased as needed to 3 mg/24 hours  
| • Adverse events*: Application and installation site reaction†, asthenic conditions†, disturbances initiating and/or maintaining sleep†, headache, nausea, somnolence† |
| DA Agent-Specific Side Effects | • AM rebound  
| • Augmentation (Shifting of symptoms to 2 hours or earlier than typical occurrence prior to treatment and extending to previously unaffected parts) |

Gabapentin Enacarbil

• 300 or 600 mg with food at 5pm
• Available in 300 mg and 600 mg extended release tablets
• Dosage adjustment in patients with compromised renal function
  – Creatinine clearance (CrCl) 30 to 59 mL/min: 600 mg on day 1 and 3 and every day thereafter
  – CrCl <30 mL/min or on hemodialysis: Not recommended
• Side effects
  – Somnolence/sedation
  – Dizziness
Hypersomnolence Disorder

A. Self-reported excessive sleepiness (hypersomnolence) despite ≥ 7 h sleep with at least one of:
   1. Daily sleep or lapses into sleep
   2. Sleep period > 9 h/day and nonrestorative
   3. Difficulty being fully awake after abrupt awakening
B. Hypersomnolence ≥ 3 times/wk and ≥ 3 mo
C. Significant distress or impairment
D. Not better explained by and does not occur exclusively during another sleep disorder, not attributable to the physiological effects of a substance and coexisting mental and medical disorders do not adequately explain it
E. Specify if:
   1. With mental disorder, including substance use disorders
   2. With medical condition
   3. With another sleep disorder

DSM-5, American Psychiatric Association, 2013
Cognitive Effects of Excessive Sleepiness

- Slower response time
- Errors of omission and commission
- Decline in memory
- Reduced learning
- Diminished concentration
- Lapses in attention due to microsleeps
- Diminished insight into subtle meanings
- Diminished subjective awareness

A. Recurrent irrepressible need to sleep ≥ 3 times/wk over the past 3 months

B. At least one of the following:
   1. Cataplexy
   2. Hypocretin deficiency
   3. Nocturnal polysomnography showing REM latency ≤ 15 min or multiple sleep latency test (MSLT) showing a mean sleep latency ≤ 8 min > 2 sleep-onset REM periods
## Psychiatric Comorbidity in Narcolepsy

<table>
<thead>
<tr>
<th>CCS Level 2 Category</th>
<th>Control (N=46,559)</th>
<th>Narcolepsy (N=9312)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>5,554 (11.9)</td>
<td>2,333 (25.1)</td>
<td>&lt;0.0001</td>
<td>2.5 (2.4, 2.7)</td>
</tr>
<tr>
<td>Mood disorders</td>
<td>6,407 (13.8)</td>
<td>3,525 (37.9)</td>
<td>&lt;0.0001</td>
<td>4.0 (3.8, 4.2)</td>
</tr>
</tbody>
</table>

P: Conditional Chi-square test; accounts for matching
Behavioral Interventions

• Have limited efficacy by themselves (e.g. napping, improving sleep habits)

• Sleepiness / fragmented nocturnal sleep is exacerbated by:
  – Poor sleep hygiene
  – Shift work
  – Alcohol and other recreational drugs

• Avoid driving and dangerous work when sleepy

# AASM Practice Parameter Guidelines for Treatment of Narcolepsy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Uses</th>
<th>Recommendation Level</th>
<th>Based On:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil</td>
<td>EDS</td>
<td><strong>Standard</strong></td>
<td>4 level 1 studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 level 2 studies</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>Cataplexy, EDS</td>
<td><strong>Standard</strong></td>
<td>3 level 1 studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 level 2 studies</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>EDS</td>
<td><strong>Guideline</strong></td>
<td>3 level 2B studies</td>
</tr>
<tr>
<td>d-amphetamine</td>
<td></td>
<td></td>
<td>4 level 5C studies</td>
</tr>
<tr>
<td>Methamphetamine*</td>
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<tr>
<td>Methylphenidate</td>
<td>EDS</td>
<td><strong>Guideline</strong></td>
<td>3 level 2B studies</td>
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<td></td>
<td></td>
<td></td>
<td>4 level 5C studies</td>
</tr>
<tr>
<td>Selegiline*</td>
<td>EDS, cataplexy</td>
<td><strong>Option</strong></td>
<td>2 level 2B studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 level 4C studies</td>
</tr>
</tbody>
</table>

*Not FDA indicated for this use

AASM, American Academy of Sleep Medicine.
Armodafinil

- Isomer of modafinil (R-modafinil)
- Indicated for EDS in narcolepsy
- Once per day formulation
- Dose: 50 mg, 150 mg, 200 mg, and 250 mg
- No effect on cataplexy or other ancillary symptoms of narcolepsy
- Can reduce efficacy of oral contraceptives
  - Increases metabolism of ethinylestradiol
- Rarely, can cause serious rashes and allergic reactions
- Side effects: headache, nausea, dizziness, insomnia

Sodium Oxybate

• Indicated for the treatment of excessive sleepiness and cataplexy in narcolepsy
• Can reduce vivid dreams, nightmares, and hypnagogic hallucinations*
• Improves nocturnal sleep*
  – Increases SWS
  – Reduces arousals and awakenings
• Precautions: use in depression; do not use with hypnotics, CNS depressant medications, and alcohol; caution patients on salt restriction; respiratory depression risk; do not use in untreated OSA
• Side effects: dizziness, vomiting, somnolence, enuresis, tremor
• Contraindications: succinic semialdehyde dehydrogenase deficiency; in combination with sedative hypnotics or alcohol

SWS, slow-wave sleep. *Not FDA indicated for this use
Antidepressants for Narcolepsy

- Can be effective for cataplexy*
- NRIs are most effective, eg, atomoxetine, venlafaxine
- Can cause sexual side effects
- Can disturb nocturnal sleep
- Have not been demonstrated to be effective for other REM phenomena, eg, hypnagogic hallucinations, sleep paralysis
- Have not been demonstrated to be effective for sleepiness

*Not FDA indicated for this use

NERI, norepinephrine reuptake inhibitor.

Amphetamines and Stimulants

• CNS stimulants; stimulate norepinephrine release and dopaminergic activity
• Side effects: Weight loss, dizziness, nausea, change in blood pressure, rapid heart beat, and headache
• Long-term side effects: Worsening of the nocturnal sleep disruption; increased risk of psychosis, paranoia, and alcohol or drug abuse; increased risk of psychiatric hospitalizations
  – Rebound hypersomnia is more common with higher doses
• High potential for abuse and development of tolerance
  – Should be administered at the lowest effective doses
• Avoid in patients with heart disease, hyperthyroidism, glaucoma, anxiety disorder, or hypertension

Obstructive Sleep Apnea Hypopnea

- OSA is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep
- Airflow cessations or reductions produce
  - Arousals
  - Fragmented sleep
  - Reductions in blood oxygen saturation
  - Fluctuations in blood pressure and heart rate

OSA Doubles the Risk of New Depressive Disorders

Medical Management

• Lifestyle changes
• Weight loss
• Body positioning devices
• PAP devices
• Oral appliances
• Nasal devices
• Medications
• Upper airway muscle strengthening
OSA and CPAP

OSA

CPAP-treated Airway
Meta Analysis of Effect of OSA Treatment on Depressive Symptoms

CPAP

Mandibular Advancement Devices

<table>
<thead>
<tr>
<th>Study ID</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amin et al 2011 [30]</td>
<td>1.51 (0.42, 2.61)</td>
<td>2.57</td>
</tr>
<tr>
<td>Sandberg et al 2001 [50]</td>
<td>2.21 (1.55, 2.86)</td>
<td>4.58</td>
</tr>
<tr>
<td>Subtotal (I-squared = 12.1%, p = 0.286)</td>
<td>2.00 (1.38, 2.62)</td>
<td>7.15</td>
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</tbody>
</table>

No baseline depression

<table>
<thead>
<tr>
<th>Study ID</th>
<th>SMD (95% CI)</th>
<th>Weight</th>
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<tbody>
<tr>
<td>Bardwell et al 2007 [31]</td>
<td>1.04 (0.18, 1.89)</td>
<td>3.49</td>
</tr>
<tr>
<td>Barnes et al 2002 [32]</td>
<td>0.01 (-0.52, 0.53)</td>
<td>5.41</td>
</tr>
<tr>
<td>Barnes et al 2004 [33]</td>
<td>0.18 (-0.13, 0.49)</td>
<td>6.87</td>
</tr>
<tr>
<td>Craig et al 2012 [35]</td>
<td>0.23 (0.01, 0.45)</td>
<td>7.42</td>
</tr>
<tr>
<td>Dierfera et al 2013 [36]</td>
<td>0.19 (-0.36, 0.74)</td>
<td>5.23</td>
</tr>
<tr>
<td>Engelman et al 1998 [37]</td>
<td>0.06 (-0.50, 0.65)</td>
<td>5.05</td>
</tr>
<tr>
<td>Engelman et al 1999 [38]</td>
<td>0.34 (-0.14, 0.82)</td>
<td>5.72</td>
</tr>
<tr>
<td>Haensel et al 2007 [39]</td>
<td>0.24 (-0.32, 0.79)</td>
<td>5.19</td>
</tr>
<tr>
<td>Jenkinson et al 1999 [41]</td>
<td>0.28 (-0.11, 0.67)</td>
<td>6.32</td>
</tr>
<tr>
<td>Lam et al 2007 [42]</td>
<td>0.12 (-0.36, 0.60)</td>
<td>5.71</td>
</tr>
<tr>
<td>Lee et al 2012 [43]</td>
<td>0.09 (-0.45, 0.62)</td>
<td>5.32</td>
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<td>Marshall et al 2005 [44]</td>
<td>-0.19 (-0.70, 0.33)</td>
<td>5.46</td>
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<tr>
<td>Montserrat et al 2001 [45]</td>
<td>0.02 (-0.56, 0.60)</td>
<td>5.05</td>
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<td>Ryan et al 2011 [49]</td>
<td>0.06 (-0.53, 0.65)</td>
<td>4.97</td>
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<tr>
<td>Siccoli et al 2008 [51]</td>
<td>0.80 (0.46, 1.30)</td>
<td>6.22</td>
</tr>
<tr>
<td>Smith et al 2007 [52]</td>
<td>-0.35 (-0.94, 0.23)</td>
<td>5.02</td>
</tr>
<tr>
<td>Yu et al 1999 [53]</td>
<td>0.00 (-0.68, 0.66)</td>
<td>4.40</td>
</tr>
<tr>
<td>Subtotal (I-squared = 29.7%, p = 0.120)</td>
<td>0.20 (0.06, 0.33)</td>
<td>92.85</td>
</tr>
</tbody>
</table>

Overall (I-squared = 71.3%, p < 0.001) | 0.31 (0.10, 0.52) | 100.00 |

Boxes: Standardized mean differences; lines: 95% CIs. Vertical solid line: no difference between treatment and control. Values to the right of the solid line favor treatment benefit. Pooled SMDs and 95% CIs are represented by the diamond shapes. Povitz M et al. (2014) .EPLoS Med 11(11): e1001762.
Surgical Alternatives

• Reconstruct upper airway
  – Nasal reconstruction
  – Uvulopalatopharyngoplasty/uvulopalatal flap
  – Genioglossus advancement
  – Hyoid advancement
  – Maxillomandibular advancement
  – Maxillomandibular expansion
  – Temperature-controlled radio frequency tongue base reduction

• Bypass upper airway – when life threatening
  – Tracheostomy

• Upper airway stimulation therapy

Circadian Rhythm Sleep-Wake Disorders

A. Persistent sleep disruption due to alteration of the circadian system or misalignment between the endogenous circadian rhythm and the sleep–wake schedule

B. Excessive sleepiness or insomnia, or both

C. Clinically significant distress or impairment functioning

D. Types
   1. Delayed sleep phase
   2. Advanced sleep phase
   3. Irregular sleep-wake
   4. Non-24-hour sleep-wake
   5. Shift work
   6. Unspecified

DSM-5, American Psychiatric Association, 2013
Circadian Rhythm Sleep-Wake Disorders

- Typical sleep phase
- Delayed sleep phase syndrome
- Advanced sleep phase syndrome
- Irregular sleep/wake syndrome
- Non-24-hour sleep/wake syndrome

Wake
Sleep

Time (24:00-16:00)
Treatment of Delayed Sleep Phase Syndrome

• Chronotherapy
  – Delay in sleep/wake times by 3 hours each

• Phase advance
  – Gradual advance of sleep/wake times
  – Phototherapy: AM, 2,000 to 10,000 lux
  – Melatonin in evening

## AASM Treatment Recommendations for Shift Work Disorder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned sleep schedules</td>
<td>Standard</td>
</tr>
<tr>
<td>Timed light exposure</td>
<td>Guideline</td>
</tr>
<tr>
<td>Timed melatonin administration</td>
<td>Guideline</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>Guideline</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Guideline</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>Guideline</td>
</tr>
<tr>
<td>Stimulants/Caffeine</td>
<td>Option</td>
</tr>
</tbody>
</table>

- **Standard**
  - High degree of clinical certainty

- **Guideline**
  - Moderate degree of clinical certainty

- **Option**
  - Uncertain clinical utility due to inconclusive or conflicting evidence

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## AASM Recommendations for OTC Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Clinical Insights</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| Melatonin | • Sleep onset & maintenance  
• Circadian phase change | • No FDA indications  
• Range of doses studied (0.5-10 mg), mostly lower doses (1.8-3 mg)  
• Hypnotic effect dependent on circadian phase  
• Little effect when endogenous levels are high | • Dizziness, headache, irritability |
| Caffeine | • Alertness          | • No FDA indications                                                             | • Diuresis, insomnia, irritability, tachycardia, headache, nervousness, GI disturbances, increased blood pressure |

FDA, US Food and Drug Administration; GI, gastrointestinal; OTC, over-the-counter.
Conclusions

- Sleep/wakefulness complaints are common in psychiatric patients, and independently contribute to morbidity.
- A systematic evaluation is warranted to identify comorbidities.
- Whenever possible, treatment should be tailored to the specific etiological abnormality.
ARS POST QUESTIONS