I’m so tired I can’t sleep: A systematic approach to the diagnosis and treatment of insomnia

Justin A. Malone MD, FAAN
Diplomate ABPN, ABEM, NBPAS
Basic Sleep Overview

Justin A. Malone MD, FAAN
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Sleep Disorders

A nurse practitioner who works at local clinic and picks up an occasional night shift in a local ED worked the 11pm to 7am shift last night. Today while trying to pay attention at the MONA conference they are relying on strong coffee to try and help stay awake.

The caffeine in the coffee the nurse practitioner took to try and stay awake affects:

A. Melatonin
B. Serotonin
C. Adenosine
D. Gamma-hydroxybutyric acid
Sleep Disorders

- Circadian rhythm disorders
- Insomnia
- Sleep related breathing disorders
- Hypersomnolence unrelated to SRBD
- Parasomnias
- Sleep-related movement disorders
Sleep Disorders

Table 3—ICSD-2 Insomnia Diagnoses

ICSD-2 Sleep Disorder Categories:
Insomnias
- Sleep Related Breathing Disorders
- Hypersomnias of Central Origin
- Circadian Rhythm Disorders
- Parasomnias
- Sleep Related Movement Disorders
- Isolated Symptoms
- Other Sleep Disorders

Insomnias (specific disorders)
- Adjustment (Acute) Insomnia
- Behavioral Insomnia of Childhood
- Psychophysiological Insomnia
- Paradoxical Insomnia
- Idiopathic Insomnia
- Inadequate Sleep Hygiene
- Insomnia Due to Mental Disorder
- Insomnia Due to Medical Condition
- Insomnia Due to Drug or Substance
- Insomnia Not Due to Substance or Known
- Physiological Condition, Unspecified
- Physiological (Organic) Insomnia, Unspecified
Sleep Pathophysiology

Nature 497, pp. S2-s3, May 2013
## Sleep Pathophysiology

### Systems Generating Wakefulness

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>Ascending reticular formation</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Substantia nigra</td>
</tr>
<tr>
<td>Hypocretin</td>
<td>Hypothalamus (perifornical)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Locus ceruleus</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Raphe nuclei</td>
</tr>
<tr>
<td>Histamine</td>
<td>Tuberomammillary nucleus</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Basal forebrain</td>
</tr>
</tbody>
</table>
# Sleep Pathophysiology

## Systems Generating Sleep

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA</td>
<td>VLPO, hypothalamus and basal forebrain</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Basal forebrain</td>
</tr>
<tr>
<td>Glycine</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>PPT/LDT (pons) and basal forebrain</td>
</tr>
</tbody>
</table>
# Sleep Pathophysiology

## Neurotransmitters of Sleep

<table>
<thead>
<tr>
<th></th>
<th>Wake/REM</th>
<th>N-Rem</th>
<th>Origin</th>
<th>Projections</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA</td>
<td>(---)/+</td>
<td>+++</td>
<td>(bs)ARAS, thal., h.thal., b. forebrain, cortex</td>
<td>p. hypo., ARAS, thalamus</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Increase w/ wakefulness/+++</td>
<td>++++</td>
<td>Diffuse cortical by-product of wake state</td>
<td>Brain stem &amp; b. forebrain cholinergic cells</td>
</tr>
<tr>
<td>Histamine</td>
<td>++++/+</td>
<td>++</td>
<td>Tubero-infundibular (post. Hypo.)</td>
<td>Thalamus, brain stem</td>
</tr>
<tr>
<td>ACH</td>
<td>++++/+++</td>
<td>+</td>
<td>LDT/PPT</td>
<td>Thal., P.Hypothal., B. Forebrain</td>
</tr>
<tr>
<td>NE</td>
<td>+++/(-)</td>
<td>++</td>
<td>LC</td>
<td>Cortex, hippocampus, thalamus, hypothalamus</td>
</tr>
<tr>
<td>SE</td>
<td>+++/(-)</td>
<td>+</td>
<td>DRN</td>
<td>Same as NE</td>
</tr>
<tr>
<td>Orexin</td>
<td>++++/?</td>
<td>+</td>
<td>Lat. &amp; post. Hypothalamus</td>
<td>LC, DRN, LDT, PPT</td>
</tr>
</tbody>
</table>
Polysomnogram
Polysomnogram

Key EEG features of NREM Sleep

- Awake (Eyes Open)
- Awake (Eyes Closed)
- NREM Stage N1
- NREM Stage N2
- NREM Stage N3 (Slow-wave sleep)
- REM Sleep

Human sleep stages:

- Alpha rhythm
- Vertex waves
- Sleep spindles
- Saw-tooth waves
Polysomnogram Histogram
Actigraphy
Sleep and aging

- **Newborn**
  - 24 HOURS
  - High level of REM sleep may help brain development

- **Child**
  - 24 HOURS
  - Children spend more time in slow-wave sleep than adults, and the intensity of this electrical activity is linked to how well they learn

- **Teenager**
  - 24 HOURS
  - Lack of slow-wave sleep can hamper learning ability

- **Adult**
  - 24 HOURS
  - Slow-wave sleep declines as the ageing brain loses grey matter from the medial prefrontal cortex, with adults less able to lay down new memories
Why is sleep important?

*Effects of sleep deprivation on cardiovascular system:*

Increased blood pressure and sympathetic nervous system activation
Increased levels of C reactive protein
Experimental sleep deprivation leads to changes in autonomic function, inflammation, and hormones that could contribute to cardiovascular disease

Prog Cardiovasc Dis 2009; 51:294-302
Why is sleep important?

Laugsand LE et al., Eur Heart J, 2013
Why is sleep important?

*Effects of sleep loss on inflammation/immunity:*

Sleep loss alters immune responses
Reduced natural killer cell activity
Changes in circulating levels of leukocytes and cytokines
Decreased antibody titers to influenza vaccinations
Increased inflammatory markers (CRP)

J. Clin Sleep Med 2007;3(5):519-528
Why is sleep important?

*Decreased sleep associated with obesity:*

**Children:** Int J. Obes Relat Metab Disord 2002; 26:710-6  
**Young Adults:** Sleep 2004; 27: 616-6  
**Older Adults:** Int. J Obesity 2008; 32:1825-34  
**Sleep restriction increases appetite:** Ann Intern Med 2004; 141(11):846-50  
**Sleep restriction decreases adipose weight loss during dieting:** Ann Intern Med 2010;153:435-441
Why is sleep important?

Sleep deprivation and accidents:

Sleep deprivation causes at least 10-15% of accidents: Sleep 2004; 27:224

Medical interns made significantly more serious medication and diagnostic errors when working shifts longer than 30 hours: NEJM 2004; 351:1838-48
Why is sleep important?

| Risk of Motor Vehicle Accidents increased after Extended Shifts | Rates per 1000 commutes |
|---|---|---|
| | Work shift ≥24 hours | Work shift <24 hours | Odds Ratio |
| Crashes | 1.07 | 0.40 | 2.3 (1.6-3.3) |
| Near-misses | 36.42 | 6.41 | 5.9 (5.4-6.3) |
| # Commutes | 54,121 | 180,289 | |

NEJM 2005; 52:125-134
Why is sleep important?

Sleep Deprivation and Diabetes:

Shorter sleep duration predicts diabetes risk: Diabetes Care 2006;29(3):657-661

Slow wave sleep deprivation increases insulin resistance: PNAS USA 2008;105:1044-49
Physiologic effects of sleep loss

Increased evening cortisol
Increased sympathetic activation
Decreased thyrotropin
Decreased glucose tolerance
Decreased leptin
Increased ghrelin

These effects alter signaling of hunger and appetite and promote weight gain, obesity, and insulin resistance

Endocrin Dev 2010; 17:11-21
Pathways for sleep loss effects on obesity and diabetes

Ann NY Acad Sci 2008; 1129:287-304
Why is sleep important?

Sleep deprivation effects on learning and memory

Sleep is important both before learning (acquisition of information) and after learning (encoding and consolidation of information)

Effects of sleep loss may vary depending on the type of material being learned
Why is sleep important?

Performance lapses increase with sleep loss

Arch. Ital Biol 2001; 139:253-67
Why is sleep important?

Sleep after learning enhances motor memory

Sleep Med, 2008; 9:S29-34
Why is sleep important?

Sleep Med, 2008; 9:S29-34
Insomnia Overview

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Diplomate ABPN, ABEM, NBPAS
Insomnia

A 60-year-old woman presents to your office with a 5-year history of difficulty falling asleep. She admits that she has always been a light sleeper, just like her mother, but her sleep problems really began 5 years ago when her husband died suddenly. During the acute grief phase she had trouble going to sleep and found that she was afraid to be in the house alone. She started leaving most of the lights on in the house, including several table lamps in the bedroom. She moved the TV into the bedroom “to take my mind off of things.” She started allowing her 80-lb. Labrador to sleep with her “to keep me company.” She often has a highball at night to help her relax. She claims that she has been “getting by” but the past 6 months have seen further deterioration in her sleep and she is only sleeping 4-5 hours per night.

Which of the following are contributing to this patient’s difficulty with sleep:

A. Co-morbid insomnia
B. Poor sleep hygiene
C. Insomnia caused by a CNS depressant
D. All of the above

Adapted from Kryger’s Sleep Medicine Review
Insomnia

Pathophysiology
A hyperarousal disorder causing an inability to relax

Exaggerated reactions to environmental stressors
Bedtime anxiety - “Worried about sleep”
Increased Brain metabolic activity
Hypothalamic-pituitary-adrenal axis
Corticotropin-releasing hormone
Increased cortisol and ACTH in sleep
Decreased GABA levels based on MRS imaging
Insomnia

Diagnostic criteria: The 3 D’s

Difficulty initiating or maintaining sleep
Despite adequate opportunity for sleep, resulting in
Daytime impairment

Acute/Short Term: Less than 3 months
Chronic: Lasts at least 1 month
Insomnia

Epidemiology and Risk Factors
Insomnia is the most common sleep disorder
One of the most prevalent mental health disorders

Challenge: Demarcate the border between insomnia complaints and clinical insomnia
Insomnia

Epidemiology and Risk Factors

26% of people complain of difficulty sleeping at least a few nights per week
42% of people complain of difficulty staying asleep
13% of people complaining of insomnia seek professional treatment: typically based on severity and advanced age

A sleep complaint does not itself arise to the standard of clinical insomnia.
Insomnia

Demographics
30-50% of American adults experience insomnia during a one-year period
10-15% of general population may have chronic insomnia

More Prevalent In:
Females
Singles
Unemployed

Ethnicity
More common in African Americans than Whites
More common in Japanese population

Socioeconomics
Lower socioeconomic status
Insomnia

Types

Sleep onset
Sleep-maintenance
Early morning awakening
Combination

Primary or Comorbid with another medical condition
Insomnia

Core Symptoms
At least 1 sleep symptom and 1 wake symptom

Sleep Symptoms
Difficulty initiating or maintaining sleep
Early morning awakening
Nonrestorative or non refreshing sleep
Insomnia

Core Symptoms
At least 1 sleep symptom and 1 wake symptom

Wake Symptoms
Sleep-associated daytime impairment:
Sleepiness
Fatigue
Mood disturbance
Cognitive difficulties
Social impairment
Occupational impairment
Insomnia

Etiology
Co-Morbid: 90%
Primary:
Adjustment
Psychophysiological (conditioned insomnia)
Paradoxical (sleep-state misperception)
Idiopathic (childhood onset)
Poor sleep hygiene

30% of chronic insomniacs may develop alcohol abuse
Insomnia

Subtypes

Acute/Adjustment insomnia
Chronic Insomnias
Insomnias secondary to/comorbid with *(90% of all insomnia)*
Insomnia

Subtypes

Acute/Adjustment insomnia
Precipitated by an identifiable stressor
One year prevalence in general population is 15-20%
More common in women and older adults
Lasts no more than 3 months
Insomnia

Subtypes

Chronic insomnias

Primary Insomnia

Learned sleep-preventing associations
Extreme concern with inability to sleep and consequences which follow
Heightened state of arousal during the day (frequently unable to nap)
Often sleep better away from home
1-2% of general population
Insomnia

Subtypes

Chronic insomnias

Paradoxical Insomnia: Sleep-state misperception

Daytime impairment much less severe than expected from the patient’s report of extreme sleep deprivation

Mismatch between PSG or actigraphy and subjective sleep estimates

Increased risk and association of/with depression, anxiety, hypnotic use/abuse
Insomnia

Subtypes

Chronic insomnias
Idiopathic Insomnia
Onset during childhood with lifelong sleep difficulty and often no identifiable precipitating event
Periods of sustained remission not reported
Insomnia

**Subtypes**

**Chronic insomnias**
**Inadequate sleep hygiene**
Patients adopt living activities inconsistent with quality sleep
Varying bedtimes
Frequent napping, especially in the evening time
Abuse of substances interfering with sleep, especially close to bedtime (alcohol, caffeine, nicotine)
Engaging in stimulating activities close to bedtime
Sleep environment no conducive to sleep (noise, light, etc.)
Insomnia

Subtypes

Chronic insomnias
Insomnias secondary to/comorbid with:
Medical conditions (pain, asthma, GERD)
Specific sleep related disorders (PLMS, OSA, SRBD)
Psychiatric disorders
Drug or alcohol abuse
Insomnia

Causes of Insomnia: Clues
Acute stressor: Adjustment insomnia
Lifelong insomnia: Idiopathic insomnia
Bad habits: Inadequate sleep hygiene
Very minimal/no sleep for several days: paradoxical insomnia
Rumination and intrusive thoughts: Psychophysiologic insomnia
Insomnia Evaluation

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Insomnia

A 17-year-old high school senior presents for evaluation with his mother because of his “insomnia” and excessive daytime somnolence. He goes to bed at midnight, but he can’t fall asleep until around 2 am and must get up at 6:30 am to make his first AP class at 7:45 am. He is very tired during the day and often inadvertently falls asleep in class. He admits that on weekends or during vacation, he stays up as late as he wants and then he doesn’t seem to have trouble falling asleep. Because he can sleep as long as he wants (often 9 or 10 hours), he then doesn’t feel tired during his wake period.

What is the most likely diagnosis?

A. Narcolepsy
B. Adjustment insomnia
C. Psychophysiologic insomnia
D. Delayed sleep phase disorder

Adapted from Kryger’s Sleep Medicine Review
Insomnia

Defining insomnia is a complex task
Symptoms v. Disorder v. Both
Often evolves over time
Heterogeneous

**Acute**  less than 1 month

**Intermittent**

**Chronic**  6 or more months
Insomnia

Multitude of Trials and Review of Literature from the 1980s and 1990s

Research Diagnostic Criteria: Universal Definition for Insomnia Disorder

Patient must report difficulty initiating or maintaining sleep, waking up too early, or chronically nonrestorative or poor-quality sleep.

Sleep difficulty occurs despite adequate opportunity and circumstances for sleep.

Patient must report sleep–related daytime impairment involving one or more the following:
- Fatigue or malaise
- Attention, concentration, or memory problems
- Social or vocational dysfunction or poor school performance
- Mood disturbance or irritability
- Daytime sleepiness
- Reduced motivation, energy, or initiative
- Proneness for errors or accidents at work or while driving
- Tension headaches, and/or gastrointestinal symptoms in response to sleep loss
- Concerns or worries about sleep

Sleep 2004; 27:1567-1596
Insomnia

Evaluation

Self-Reporting: Problematic
Retrospective
Biased
Recall errors
Insomnia

Evaluation

*Prospective Sleep Diaries*

**Definition:** Sleep diary data that collects information on sleep from the night just completed

2 weeks is recommended

**Should record:**

Sleep-onset latency
Wake time after sleep onset
Number of awakenings
Total sleep time

Helps elucidate sleep efficiency and type of insomnia (onset, maintenance, terminal).
### Insomnia

**Examples**

<table>
<thead>
<tr>
<th>Day of the week</th>
<th>Monday</th>
<th>Sun</th>
<th>Mon</th>
<th>Tues</th>
<th>Wed</th>
<th>Thur</th>
<th>Fri</th>
<th>Sat</th>
<th>For clinic use only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calendar date</td>
<td>3/25/66</td>
<td>8/3</td>
<td>8/4</td>
<td>8/5</td>
<td>8/6</td>
<td>8/7</td>
<td>8/8</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>1. Yesterday I napped from ___ to ___ (note time of all naps)</td>
<td>1:30-2:45 pm</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1:30-2:15 pm</td>
</tr>
<tr>
<td>2. Last night I took ___ mg of ___ or ___ of alcohol as a sleep aid.</td>
<td>Ambien 5 mg</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3. Last night I turned off the lights and attempted to fall asleep at ___ (AM or PM)?</td>
<td>11:30 PM</td>
<td>11:00 PM</td>
<td>11:30 PM</td>
<td>10:50 PM</td>
<td>11:00 PM</td>
<td>11:00 PM</td>
<td>10:30 PM</td>
<td>11:30 PM</td>
<td></td>
</tr>
<tr>
<td>4. After turning off the lights it took me about ___ minutes to fall asleep.</td>
<td>40 min</td>
<td>25 min</td>
<td>35 min</td>
<td>20 min</td>
<td>45 min</td>
<td>60 min</td>
<td>20 min</td>
<td>35 min</td>
<td></td>
</tr>
<tr>
<td>5. I woke from sleep ___ times. (Do not count your final awakening here.)</td>
<td>2 times</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6. My awakenings lasted ___ minutes. (List each awakening separately.)</td>
<td>25 min</td>
<td>40 min</td>
<td>35 min</td>
<td>25 min</td>
<td>45 min</td>
<td>20 min</td>
<td>20 min</td>
<td>10 min</td>
<td>60 min</td>
</tr>
<tr>
<td>7. Today I woke up at ___ (AM or PM). NOTE: This is your final awakening.</td>
<td>6:30 AM</td>
<td>7:00 AM</td>
<td>6:30 AM</td>
<td>6:30 AM</td>
<td>7:00 AM</td>
<td>6:45 AM</td>
<td>6:30 AM</td>
<td>8:15 AM</td>
<td></td>
</tr>
<tr>
<td>8. Today I got out of bed for the day at ___ (AM or PM)</td>
<td>7:15 AM</td>
<td>7:00 AM</td>
<td>7:00 AM</td>
<td>6:30 AM</td>
<td>7:30 AM</td>
<td>7:15 AM</td>
<td>7:00 AM</td>
<td>9:00 AM</td>
<td></td>
</tr>
<tr>
<td>9. I would rate the quality of last night’s sleep as:</td>
<td>1 = very poor</td>
<td>4 = good</td>
<td>2 = poor</td>
<td>5 = excellent</td>
<td>3 = fair</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1. Not at all rested</td>
<td>4 = well rested</td>
<td>2 = slightly rested</td>
<td>5 = somewhat rested</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. When I woke up today I felt;</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

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Principles and Practice of Sleep Medicine 5th ed.
## Insomnia

### 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 (|) 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 7:30 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>1 pm</th>
<th>2 pm</th>
<th>3 pm</th>
<th>4 pm</th>
<th>5 pm</th>
<th>6 pm</th>
<th>7 pm</th>
<th>8 pm</th>
<th>9 pm</th>
<th>10 pm</th>
<th>11 pm</th>
<th>Midnight</th>
<th>1 am</th>
<th>2 am</th>
<th>3 am</th>
<th>4 am</th>
<th>5 am</th>
<th>6 am</th>
<th>7 am</th>
<th>8 am</th>
<th>9 am</th>
<th>10 am</th>
<th>11 am</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Mon.</td>
<td>Work</td>
<td>E</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

---

**Principles and Practice of Sleep Medicine 5th ed.**
Insomnia

Evaluation

Actigraphy may be useful in some cases

PSG and MSLT not indicated in the routine evaluation of chronic insomnia unless suspect primary sleep disorder: RBD, PLMS, SRBD, Narcolepsy
Insomnia

Prevalence
Depends on Definition and Subtype

Comorbid is most common

Primary is less common
Insomnia

Comorbid insomnia is a symptom secondary to another disorder. 2005 NIH State-of-the Science Consensus panel recommended that the term comorbid insomnia replace the term secondary insomnia.

Felt to account for up to 90% of insomnia in the general population
20% of people with insomnia demonstrate clinically significant depression
19.3% of people with insomnia demonstrate clinically significant anxiety
Insomnia

Comorbid insomnia

Most Common:
Psychiatric disorders 77%
Anxiety
Depression
Panic disorder
Adjustment disorder
Somatoform disorder
Personality disorders

Principles and Practice of Sleep Medicine 5th ed.
## Insomnia

### Comorbid insomnia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Disorders</td>
<td>%</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>22</td>
</tr>
<tr>
<td>Cancer</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>7</td>
</tr>
<tr>
<td>Breathing difficulty</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>50</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>34</td>
</tr>
</tbody>
</table>

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Insomnia

Three P Model

Predisposing Factors
Light sleepers
Anxiety
Relationship Problems

Precipitating Factors
Event/Stress which overwhelms coping mechanisms
Bereavement
Loss of job

Perpetuating Factors
Maladaptive behaviors
Misconceptions regarding sleep
Persistent sleep hygiene issues, or learned sleep-preventing associations
Insomnia

Three P Model

Principles and Practice of Sleep Medicine 5th ed.
Insomnia

Evaluation

Medication Precipitants
Antidepressants (SNRIs)
Beta-blockers - propranolol
Bronchodilators
Decongestants
Corticosteroids
Stimulants
Insomnia

Evaluation

Remember the 3 Ps
Look for comorbid precipitants (90% of all causes of insomnia)
Try and correct accordingly
Pharmacology and Sleep

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Diplomate ABPN, ABEM, NBPAS
Pharmacology

A 62-year-old man with a history of RLS is referred to you because of a recent intensification of his symptoms. His symptoms typically begin around 6pm and can be so uncomfortable that he soaks in a hot tub for about an hour prior to bedtime. He recently started taking an antidepressant to help him cope with the death of a close relative.

Which of the following antidepressants is least likely to increase RLS and PLMS type symptoms?

A. Bupropion
B. Mirtazapine
C. Trazodone
D. Imipramine
E. Fluoxetine
F. Venlafaxine

Adapted from Kryger’s Sleep Medicine Review
Insomnia

Antidepressants

Sedation
Tricyclic: Amitriptyline, Doxepin
Mirtazapine
Trazodone
Paroxetine

Alerting
Fluoxetine
Sertraline
SNRIs: Venlafaxine
Insomnia

Somnambulism

Hypnotics: benzodiazepines and BzRAs especially zolpidem
Lithium
Major tranquilizers such as phenothiazines
GABA, sodium oxybate
Antihistamines
Stimulants
Anticholinergics
Montelukast
Alcohol
Insomnia

Nightmares
TCAs
SSRIs
SNRIs
Bupropion
Beta-Blockers, atenolol less likely
Alpha 2-agonists such as clonidine
Reserpine
Hypnotics
Barbiturates
Chloral hydrate
Stimulants
First Generation Antipsychotics
Erythromycin
Plaquenil

Quinolones
Zanamivir
Peramivir
Withdrawal of REM suppressing agents
Bupropion
Chantix
Amiodarone
Insomnia

Abnormal Dreams
BzRAs
Levodopa
Ropinirole
Pramipexole
Singulair
Donepezil
Insomnia

REM Behavior Disorder
SSRIs
SNRIs especially venlafaxine
Mirtazapine
MAOIs
TCAs
Stimulants: caffeine, amphetamines, cocaine
EtOH

*Bupropion is not associated with RBD
**Insomnia**

**RLS/PLMS**
- Antidepressants
  - SSRIs
  - SNRIs
  - TCAs
  - Mirtazapine
  - Lithium
- Dopamine antagonists - antiemetics, antipsychotics
- Older sedating antihistamines
- Calcium channel antagonists
- Tramadol

**Methylxanthines**
- Corticosteroids
- Opioid withdrawal
- Caffeine
- Nicotine
- Alcohol

*Bupropion does not cause RLS*
### Insomnia

#### Effects of Alcohol on Sleep

**Diagram:**
- **(a) No alcohol**
  - Wake-promoting systems
  - BF cholinergic neurons
  - BF GABAergic neurons
  - BF Glutamatergic neurons
  - Hypocretin neurons
  - Monoaminergic neurons
- **(b) After alcohol consumption**
  - Sleep-promoting systems
  - MePN GABAergic neurons
  - VLPO GABAergic neurons
  - PZ GABAergic neurons
  - PF-LHA MCH/GABAergic neurons

**Key:**
- Adenosine $A_1$ receptor
- Adenosine $A_2A$ receptor
- Adenosine
- Alcohol
- ENT1
- Activation

*Alam, McGinty, Journal of neurochemistry 2017*
Insomnia

Effects of Alcohol on Sleep
Biphasic effect on sleep and waking

*Stimulating*
At low doses and on the rising phase of alcohol levels
Visualize an animated person having fun at a bar

*Sedating*
At high doses and on the falling phase of alcohol levels
Visualize a drowsy person after drinking too much
Insomnia

Effects of Alcohol on Sleep

Rapid Metabolism
Sedating effect wears off as adenosine levels decrease and this disrupts the normal sleep pattern leading to increased nocturnal awakenings and poor sleep efficiency
Insomnia

Effects of Alcohol on Sleep

Acute Intoxication

Decreased sleep latency

During first half of night

- Increased NREM
- Decreased REM
- Increased TST

During second half of night

- Increased wakefulness due to rapid EtOH metabolism
- REM rebound
- Increased dreaming
- Sympathetic arousal
Insomnia

Effects of Alcohol on Sleep

Alcoholic Dependency
Increased sleep latency
Decreased total sleep time
Fragmented sleep, especially second half of the night
Decreased REM
Circadian rhythm disruption when EtOh consumed throughout the day
Insomnia

Effects of Alcohol on Sleep

Acute withdrawal in alcohol dependence

Insomnia
Decreased sleep continuity
Decreased TST
Decreased SWS
REM rebound
Nightmares
Insomnia

Effects of Alcohol on Sleep

Prolonged effects of withdrawal
May last as long as 1-2 years
Decreased TST
Decreased SWS
Increased REM
Insomnia Treatment Options

Justin A. Malone MD, FAAN
Diplomate ABPN, ABEM, NBPAS
Insomnia

In conversation with our 60-year-old woman with multiple sleep complaints and risk factors (Co-morbid insomnia, poor sleep hygiene, alcohol use) we recommend which of the following treatment options to best try and help improve her quality of life?

A. Cognitive Behavioral Therapy for Insomnia (CBT-I), Sleep Hygiene, and Pharmacologic Therapy
B. CBT-I and Sleep Hygiene
C. Start with sleep hygiene alone
D. Start with CBT-I alone
E. Start with Pharmacologic Therapy alone
Insomnia

Treatment Options

Cognitive-behavioral therapy for insomnia (CBT-I) strategies:
Often performed under the guidance of a psychologist experienced in these strategies
Short-term benefits are comparable to pharmacologic therapy
Long-term benefits are more effective than pharmacotherapy
Focusing on patients with comorbid medical disorders and psychiatric disorders

Pharmacological Therapies
Insomnia

Most effective CBT-I

Stimulus-control therapy
Attempts to reassociate the bedroom environment with healthy sleep
Bedtime only when sleepy
Use the bed only for sleep and intimacy
Curtail wake time in bed
If unable to sleep within 15-20 minutes (estimate) of nocturnal wakening, relax or negative in quiet activity in another room and return to bed when sleepy.
Avoid clock watching - Remove or turn around

Sleep-restriction therapy
Aim is to improve sleep onset through sleep deprivation
Being by reducing the time in bed according to the estimated time spent asleep (diary)
Establish a regular wake time and advance bedtime when 90% sleep efficiency is achieved
Insomnia

Stimulus-control therapy

Principles and Practice of Sleep Medicine 5th ed.
Insomnia

Other CBT-I

Progressive muscle relaxation (PMR)
Patient taught to systematically relax each part of the body

Biofeedback
Complex procedure that requires an experienced operator

Cognitive therapy
Re Educates patients faulty beliefs and attitudes to sleep
Correct irrational fears, unrealistic expectations, and excessive concern about the amount of sleep time needed for adequate daytime function.
Insomnia
Other CBT-I

Relaxation therapy
Aims to decrease anxiety and lower arousal threshold
Hot bath prior to bedtime helps relaxation and increases core temperature to promote sleep during its subsequent decline
Breathing exercises, meditation, modified yoga, guided imagery
Insomnia

Sleep hygiene education

Understanding and educating patients about the circadian rhythm
Adjusting bedroom environment, cool, quiet, absent TV, lower lighting
Establish a regular “wind down” routine - establish good habits
Avoiding stimulants or activities preventing sleep onset
Reduce or eliminate products that interfere with sleep (caffeine, nicotine, alcohol)
Avoid/eliminate napping, especially in the evenings
No exercising or large meals close to bedtime (3h.)
Insomnia

Sleep hygiene education

CIRCADIAN RHYTHMS

WAKE
SLEEP

Melatonin  
Cortisol  
Core Body Temp

Cortisol
Melatonin

6am  9am  12pm  3pm  6pm  9pm  12am  3am  6am  9am
Insomnia

Sleep hygiene education
Insomnia

Pharmacologic - Nature 497, pp. S2-s3, May 2013
# Insomnia

## Pharmacologic

### Drugs Indicated for Insomnia

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>$T_{1/2}$ (Hours)</th>
<th>Dose (mg)</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>48-120</td>
<td>15-30</td>
<td>BZD</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>8-20</td>
<td>15-30</td>
<td>BZD</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>2-6</td>
<td>0.125-0.25</td>
<td>BZD</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Prosom</td>
<td>8-24</td>
<td>1-2</td>
<td>BZD</td>
</tr>
<tr>
<td>Quazepam</td>
<td>Doral</td>
<td>48-120</td>
<td>7.5-15</td>
<td>BZD</td>
</tr>
<tr>
<td>Zolpidem$^1$</td>
<td>Ambien</td>
<td>1.5-2.4</td>
<td>5-10</td>
<td>BZRA</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Sonata</td>
<td>1</td>
<td>5-20</td>
<td>BZRA</td>
</tr>
<tr>
<td>Eszopiclone$^2$</td>
<td>Lunesta</td>
<td>5-7</td>
<td>1-3</td>
<td>BZRA</td>
</tr>
<tr>
<td>Zolpidem ER$^{1,2,3}$</td>
<td>Ambien CR</td>
<td>1.5-2.4</td>
<td>6.25-12.5</td>
<td>BZRA</td>
</tr>
<tr>
<td>Zolpidem SL$^{1,3,4}$</td>
<td>Intermezzo</td>
<td>1.4-3.6</td>
<td>1.75-3.5</td>
<td>BZRA</td>
</tr>
<tr>
<td>Ramelteon$^{2,5}$</td>
<td>Rozerem</td>
<td>1.5-5</td>
<td>8</td>
<td>MT agonist</td>
</tr>
<tr>
<td>Doxepin$^{2,5}$</td>
<td>Silenor</td>
<td>15</td>
<td>3-6</td>
<td>TCA</td>
</tr>
</tbody>
</table>
Insomnia

Summary of AASM insomnia guideline treatment flowchart
Childhood Sleep Disorders

A couple presents to your office seeking help with their 24-month-old daughter’s sleep problem. The child has been a poor sleeper from birth and will not fall asleep when alone. The parents had her sleep in their bed from about 4 months of age, when nocturnal crying started to interfere with their own sleep. Attempts to let her fall asleep in her own room have been unsuccessful. She quickly will fall asleep in her parents bed. When in her crib alone she screams as if in fear. The child’s examination is normal. The child does not demonstrate any evidence of daytime sleepiness. There is no family history of a sleep disorder.

What is the most likely diagnosis of this child’s sleep problem?

A. Sleep terrors
B. Behavioral insomnia of childhood: limit-setting type
C. Behavioral insomnia of childhood: sleep-onset association type
D. Primary insomnia

Adapted from Kryger’s Sleep Medicine Review
Insomnia

Childhood Sleep

Developmental Milestones in Sleep Patterns
6 weeks: longest sleep period occurs at night
6-9 months: able to sleep through the night
3-6 years: cessation of daytime nap
Insomnia

Childhood Sleep

Total sleep time by age in hours

<1 month: 19
<1 year: 15
1-3 years: 12
3-5 years: 10
>5 years: 9
Insomnia
Childhood Sleep

**Insomnia type symptoms in children**

- Behavioral insomnia: 10-30%
- Difficulty falling asleep: 10%
- Child night wakings for various reasons: 1-10%
- Sleep onset association disorder
- Limit setting disorder
- Poor sleep hygiene
- Overlap with delayed sleep phase: weekend sleep in or late day naps
Insomnia

Childhood Sleep

Behavioral treatments of childhood insomnia
Place child to bed while drowsy but still awake: 2-4 months
Transition infant to final sleep environment: 3 months
Discontinuation of nighttime feedings: 6+ months
Sleep hygiene correction in older children same as in adults
Insomnia

Childhood Sleep

Fatal Familial Insomnia
Prion disease
Hereditary form due to a GAC to AAC mutation at codon 178 of the prion PRNP gene at chromosome 20
Classification based on methionine polymorphism at codon 129
Methionine homozygous - short disease course; duration of survival <12 months
Methionine-valine heterozygous - longer disease course; duration of survival 1-6 years
Circadian Rhythm Sleep Disorders

Justin A. Malone MD, FAAN
Diplomate ABPN, ABEM, NBPAS
Circadian Rhythm Sleep Disorders

A 27-year-old nurse began working a rotating shift about 6 months ago. Her rotation schedule was days to evenings to nights. Her schedule is to work three 12-hour days per week and then rotate to the next later shift. Initially she had no trouble adapting to this rotation, however she did report sleepiness with the overnight shifts. After a few months she found it increasingly difficult to stay awake all night. A coworker found her asleep on the job recently, and now the patient is worried about losing her job.

What is the best recommendation for this patient’s shift work sleep disorder?

A. Discontinue night shifts and work regularly scheduled daytime and/or evening shifts if possible
B. Avoid morning light after working a night shift
C. Try armodafinil for daytime sleepiness
D. Hire an attorney to sue your manager and hospital administration for making such horrible rotating schedules in the first place

Adapted from Kryger’s Sleep Medicine Review
**Insomnia**

**Circadian Rhythm Sleep Disorders**

Caused by recurrent or persistent misalignment between the desired sleep schedule and the circadian sleep-wake rhythm

Can be associated with insomnia or sleepiness, or both

Sleep diaries and actigraphy may be helpful in diagnosing and monitoring these conditions

Polysomnogram not routinely indicated
Insomnia

Circadian Rhythm Sleep Disorders

Advanced Sleep Phase Syndrome
Morning lark
Early bedtime (6-9pm) and early wake time (2-5am)
Excessive sleepiness in the later afternoon or early evening
Morning awakening is earlier than desired
Onset common during middle age and older years
Therapy: Early evening bright light
Rule out depression
Insomnia

Circadian Rhythm Sleep Disorders

Delayed Sleep Phase Syndrome
Night owl
Late bedtime (1-6am) and late wake time (10am-2pm)
Sleep onset insomnia when sleep is attempted earlier
Excessive sleepiness in the early morning
Onset often during adolescence
Therapy: Early morning light, evening melatonin
Insomnia
Circadian Rhythm Sleep Disorders

Free-Running Circadian Disorder
Progressive daily delay in sleep and wake times
Result in periodically recurring problems of insomnia or EDS
Most affected persons are totally blind
Therapy: Evening melatonin, light therapy for persons with light perception, tasimelteon a melatonin receptor agonist.
Insomnia

Circadian Rhythm Sleep Disorders

Free-Running Circadian Disorder
Insomnia

Circadian Rhythm Sleep Disorders

Irregular Sleep-Wake Rhythm
Variable, inconsistent and multiple sleep and wake periods over a 24-hour period
Most frequently seen in association with dementia or mental retardation
The “atrial fibrillation” of sleep disorders
Therapy: evening melatonin, phototherapy
Insomnia
Circadian Rhythm Sleep Disorders
Irregular Sleep-Wake Rhythm
Insomnia

Circadian Rhythm Sleep Disorders

Jet Lag
Westward travel
Phase advanced relative to new time zone
Early evening sleepiness and early morning insomnia

Eastward travel
Phase delayed relative to new time zone
Sleep onset insomnia and morning sleepiness

Therapy: phototherapy, Melatonin, Stimulants, Hypnotics
Insomnia

Circadian Rhythm Sleep Disorders

Shift Work Disorder
Factors promoting SWSD
Age
Female gender
“Morningness” circadian rhythm preference
Backward (counterclockwise) shift rotation schedule
Therapy: Avoid overnight shifts if possible, bright light exposure in the workplace, planned napping, stimulants, hypnotics if having trouble sleeping, avoid morning light after working night shifts
Summary Slides

Justin A. Malone MD, FAAN
Diplomate ABPN, ABEM, NBPAS
Summary

Am Fam Physician. 2007 Aug 15;76(4):517-526
Summary

Insomnia is common

Comorbid insomnia accounts for 90% of cases

Treatment typically requires CBT-I and Pharmacologic therapies

An understanding of the circadian rhythm and sleep hygiene principles are helpful for most individuals suffering from insomnia

Tools are readily available for the assessment and management of these patients
Summary

Summary of AASM Insomnia Guideline assessment flowchart

Principles and Practice of Sleep Medicine 5th ed.
Summary

AASM Insomnia Treatment Guideline

New Guideline
February 2017

The AASM has published a new clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults. These new recommendations are based on a systematic review of the literature on individual drugs commonly used to treat insomnia, and were developed using the GRADE methodology. The recommendations in this guideline define principles of practice that should meet the needs of most adult patients, when pharmacologic treatment of chronic insomnia is indicated. The clinical practice guideline is an essential update to the clinical guideline document:


Questions?

Justin A. Malone MD, FAAN
Diplomate ABPN, ABEM, NBPAS

Link to slides:
https://docs.google.com/presentation/d/17o75PAm2iF_RuDTkY_v1KIncC3Ew2dMSzEL4822AC90/edit?usp=sharing