Complementary & Alternative Medicines for the Treatment of Insomnia

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Learning Objectives

- Explain the proposed causes and potential complications of insomnia
- Discuss the evidence that supports and questions the use of various complementary and alternative medicines (CAM) for the treatment of insomnia
- Differentiate the effectiveness, adverse effects, precautions, and drug interactions for selected CAM used in the management of insomnia
- Based on individual patient information, recommend appropriate CAM options and monitoring parameters for the treatment of insomnia
DSM-IV Diagnostic Criteria for Primary Insomnia

- The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least one month.

- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

- The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.
DSM-IV Diagnostic Criteria for Primary Insomnia

- The disturbance does not occur exclusively during the course of another mental disorder (i.e. major depressive disorder, generalized anxiety disorder, delirium).

- The disturbance is not due to the direct physiological effects of a substance (i.e. a drug of abuse, a medication) or a general medication condition.
Impact of Sleep Impairment

- Physical fatigue
- Increased risk of falls
- Decreased memory and concentration
- Impaired psychomotor performance
- Poorer quality of life
- Increased risk of future mood, anxiety, and substance use disorders
- Societal consequences
Alcohol and Sleep Impairment

![Bar chart showing off road deviations for placebo and ethanol at 8 hours and 4 hours.]

- Placebo 8 Hours: 0
- Ethanol 8 Hours: 7
- Placebo 4 Hours: 0
- Ethanol 4 Hours: 35
Causes of Chronic Insomnia

- **Primary specific sleep disorders**
  - Circadian rhythm disorders
  - Sleep apnea
  - Restless leg syndrome

- **Physical illness**
  - Uncontrolled pain: arthritis
  - Cardiovascular: CHF, nocturnal angina
  - Pulmonary: COPD, allergic rhinitis
  - Gastrointestinal: GERD, PUD
  - Urinary: nocturia, incontinence
  - CNS: stroke, Alzheimer disease, seizure disorder
  - Psychiatric: anxiety, depression, psychosis
Causes of Insomnia (cont.)

- Behavioral
- Environmental
- Medications
  - CNS stimulants: amphetamines
  - Antidepressants: bupropion, SSRI, venlafaxine
  - Anti-Parkisonian agents: levodopa
  - Decongestants: pseudoephedrine
  - Bronchodilators: theophylline
  - Cardiovascular: Beta-blockers, diuretics
  - Antihypertensives: clonidine, methyldopa
  - Misc: corticosteroids, anticholinergics, alcohol, stimulant laxatives
Non-Pharmacological Management of Insomnia

- **Sleep hygiene**
  - Minimize random noise
  - Avoid caffeine, nicotine, alcohol
  - Avoid stimulating drugs in the evening
  - Regular exercise before evening
  - Evening fluid restriction
  - Use regular times for sleeping
  - Avoid daytime napping
  - Save bedroom for sleeping
Alternative Therapies for the Treatment of Insomnia
Types of CAM

- Biologically based approaches
  - Diets
  - Herbs
  - Vitamins
- Manipulative and body-based therapies
  - Massage
  - Chiropractic
  - Osteopathy
- Energy therapies
  - Reiki
  - Magnets
  - Qigong
- Common CAM practices
  - Yoga
  - Spirituality
  - Relaxation
- Mind-body interventions
  - Homeopathy
  - Naturopathy
  - Ayurveda
- Alternative medical systems
  - Traditional Chinese Medicine
  - Ayurveda
  - Naturopathy
CAM Usage

- Telephone survey of 1,559 people ≥ 50 years old found:
  - 54% of persons aged 65 or older had used CAM therapy or practice
  - Individuals with a higher income and more years of college education more likely to use CAM
  - CAM resources
    - Family or friends (22%)
    - Radio/TV/internet (20%)
    - Publications (14%)
    - Physician (12%)
Patients’ Reasons for Not Discussing CAM with their MDs

- MD would have been dismissive or told you not to do it: 12%
- Don't think MD knows the topic: 17%
- Not enough time during office visit: 19%
- Didn't know they should: 30%
- MD never asked: 42%
Number of Publications for CAM-based Insomnia Therapies

- Melatonin: 1800
- Acupuncture: 600
- Massage: 200
- Valerian: 100
- Meditation: 50
- Yoga: 30
- Acupressure: 20
- Tai Chi: 10
- Ayurveda: 10
Biologically-Based Approaches for the Treatment of Insomnia
Common Study Measures

- Sleep onset latency (SOL)
  - Amount of time between laying down to sleep and the onset of sleep

- Sleep efficiency (SE)
  - Amount of time spent asleep as a percentage of the total time spent in bed

- Sleep quality (SQ)
  - The perceived quality of sleep

- Wakefulness after sleep onset (WASO)
  - Amount of time spent awake in bed following the first attainment of sleep

- Total sleep time (TST)

- Percent time in REM sleep (PTR)
Melatonin

- **Metabolite of tryptophan**

- **Mechanism of action**
  - Neurohormone produced by the pineal gland
  - Low daytime circulating levels and elevated nocturnal levels
  - Dark → retina → suprachiasmatic nucleus of the hypothalamus → pineal gland → melatonin secretion → sleep induction

- **Doses**
  - 0.1 – 0.3 mg = physiologic melatonin levels
  - 5 – 10 mg = pharmacologic melatonin levels
Age Effects on Melatonin Levels

20-43 years (29.2 ± 6.5 years)  
49-73 years (60 ± 8.2 years)
Melatonin

Methods

- Multi-center, placebo-controlled trial (Singer, et al)
- Randomized 157 older adults with Alzheimer’s Disease and nighttime sleep disturbance
- 3 groups:
  - Placebo,
  - Melatonin 2.5 mg SR
  - Melatonin 10 mg

Results

- No statistically significant differences in objective sleep measures in any group.
- Non-significant trends for increased nocturnal TST and decreased WASO were observed in the melatonin groups.
- Caregivers noted improved sleep (per sleep diary) for patients using 2.5 mg SR.
Melatonin

Methods

• Meta-analysis of 14 RCTs on melatonin use for primary sleep disorders (n=279) (Buscemi et al.)
• Participant ages: 0 to ≥ 66 years
• Study duration: ≤ 1 to 4 weeks total

Results

• Melatonin significantly decreased SOL by 11.7 mins
• Greater decreases in people with delayed sleep phase syndrome compared with people with insomnia (38.8 mins vs 7.2 mins).
• Sleep efficiency was greater in the elderly population compared to younger participant (5.3% vs 0%)
# Melatonin

![Graph showing the meta-analysis of sleep onset latency in people with primary sleep disorders: melatonin versus placebo.](image-url)

**FIGURE 2.** Meta-graph of sleep onset latency in people with a primary sleep disorder: melatonin versus placebo.
Melatonin

Table 3. Results for Efficacy and Safety Outcomes: Melatonin Versus Placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Melatonin Group, n</th>
<th>Placebo Group, n</th>
<th>Summary Measure</th>
<th>Point Estimate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep onset latency</td>
<td>14</td>
<td>218</td>
<td>207</td>
<td>WMD</td>
<td>−11.7 min</td>
<td>−18.2, −5.2</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>10</td>
<td>138</td>
<td>138</td>
<td>WMD</td>
<td>2.5%</td>
<td>−0.2, 5.2</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>2</td>
<td>20</td>
<td>20</td>
<td>SMD</td>
<td>0.5</td>
<td>−0.1, 1.1</td>
</tr>
<tr>
<td>Wakefulness after sleep onset</td>
<td>6</td>
<td>88</td>
<td>88</td>
<td>WMD</td>
<td>−8.2 min</td>
<td>−28.2, 11.9</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>13</td>
<td>202</td>
<td>207</td>
<td>WMD</td>
<td>9.6 min</td>
<td>−4.7, 23.9</td>
</tr>
<tr>
<td>Percentage time in REM sleep</td>
<td>3</td>
<td>45</td>
<td>45</td>
<td>WMD</td>
<td>0.4 min</td>
<td>−1.2, 2.0</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>9</td>
<td>138</td>
<td>143</td>
<td>RD</td>
<td>0.0</td>
<td>−0.05, 0.06</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>116</td>
<td>124</td>
<td>RD</td>
<td>0.01</td>
<td>−0.04, 0.06</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>116</td>
<td>124</td>
<td>RD</td>
<td>−0.02</td>
<td>−0.06, 0.03</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>8</td>
<td>128</td>
<td>125</td>
<td>RD</td>
<td>0.01</td>
<td>−0.04, 0.05</td>
</tr>
</tbody>
</table>

WMD, weighted mean difference; SMD, standardized mean difference; RD, risk difference.
Melatonin

- **Limitations of studies**
  - Considerable heterogeneity in study results
  - Subject to variation in product quality

- **Precautions / Adverse Effects**
  - Headache (8%), nausea, dizziness (4%), drowsiness (20%)
  - Possible pro-inflammatory effects
  - May worsen sleep apnea

- **Drug interactions**
  - Calcium channel blockers: may impair antihypertensive efficacy
  - Fluvoxamine: increased CNS depression by CYP2D6 inhibition
  - Warfarin: increased risk of bleeding

- **Available products**
  - GNC Melatonin 1 mg sublingual tabs: $5.99/100 tabs
  - Natron Melatonin 3 mg tabs: $12.99/240 tabs
Melatonin Summary

- Current literature suggests melatonin may aid in the management of circadian sleep disorders

- Evidence is more equivocal for primary or secondary insomnia

- May be most appropriate for those with low melatonin levels or abnormal timing of melatonin cycle

- Relatively benign side effect profile
Valerian

- **Valerian officinalis**
  - Perennial herb

**Mechanism of Action**
- Chemical composition of valerian includes valeric acid and g-aminobutyric acid.
- Possible direct sedative effects in addition to GABA re-uptake inhibition.

**Doses**
- 400 – 900 mg/day
Valerian

Methods

• Meta-analysis of 16 RCTs (n=1093) studying valerian’s effects on inducing sleep and improving sleep quality (Bent et al).
• Doses: 225 to 1215 mg per day
• Mean age of study group: 11 to 79 years
• Mean study duration ranged from 1 to 30 days

Results

• Patients taking valerian had an 80% greater chance of reporting improved sleep compared to patients taking placebo.
• No consistent, statistically significant changes in any objective outcome measures.
Valerian

Figure 1  Meta-analysis of 6 studies reporting dichotomous outcomes for sleep quality (sleep improved or not). The dichotomous outcome (improved sleep or not) is presented as the relative risk for reporting improved sleep in the valerian group. Risk ratios greater than one indicate a benefit in the valerian group. Point estimates are represented by diamonds (with first author names) for individual studies and by squares for the summary estimates. Vertical lines represent 95% confidence intervals [CIs].
Valerian

❖ Efficacy

• Systemic review of 29 RCTs studying the efficacy and safety of valerian in the management of insomnia (Taibi et al).
• Doses: 100 to 1215 mg per day
• Mean age of study group: 26 to 74 years
• Mean study duration: 1 to 42 days

❖ Results

• No significant differences between valerian and placebo either in healthy individuals or in persons with general sleep disturbance or insomnia.
• Included most recent studies which were also the most methodologically rigorous
• No serious adverse effects occurred in these clinical trials.
Valerian

- **Limitations of studies**
  - Considerable heterogeneity in study results
  - Subject to variation in product quality
  - Dichotomous outcomes

- **Precautions/Adverse Effects**
  - Few case reports of transient liver dysfunction
  - Headache, gastrointestinal (GI) complaints, morning “hangover,” diarrhea, drowsiness, mental dullness, difficulty sleeping, mood changes

- **Drug Interactions**
  - CNS depressants (i.e. benzodiazepines, opioids): may increase sedation and decrease respiratory drive

- **Available Products**
  - Nature’s Way Valerian Root 530 mg Capsules: $6.49/100 caps
  - GNC Nature’s Fingerprint 500 mg Valerian Capsules: $7.49/100 caps
Valerian Summary

- Appears to have evidence of mild subjective improvement in sleep, especially when used for 2 weeks or more.

- Objective testing has had less consistent results with little or no improvement noted.

- Methodologic limitations, non-standardized formulations, and small sample sizes of existing literature suggests further larger studies are needed.
Problems with Alternative Products

- **Standardization**
  - Differing source of product

- **Purity**
  - 4/17 valerian products had no detectable valerian content, 4 had half the amount listed, 2 had lead contamination, and one had cadmium contamination

- **ConsumerLab.com**

*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.*
Manipulative & Body-Based Practices for the Treatment of Insomnia
Acupuncture

- Originated in China more than 2,500 years ago

- Mechanism of action (metaphysical):
  - Disease is due to an internal imbalance of yin (cold, slow, or passive principle) and yang (hot, exited, or active principle).
  - This imbalance leads to blockage in the flow of qi along meridians.
  - Qi can be unblocked by using acupuncture at meridian “intersections.”
**Acupuncture**

- **Mechanism of action (physiological):**
  - Meridians are located around core nerve endings and stimulation of these points result in neurotransmitter release

- **Rabbit vs. Heat Lamp experiment**

- **Increased melatonin secretions?**
Acupuncture

❖ Methods
  • Cochrane review of 7 RTCs involving 590 participants with insomnia
  • Participant age: 15-98 years
  • Duration of insomnia: 6 months to 19 years.

❖ Results
  • Efficacy of acupuncture was inconsistent between studies for many sleep parameters
  • The combined results from 3 studies reporting subjective insomnia improvement show that acupuncture was not more significantly effective than control (RR=1.66, 95%CI=0.68 to -4.03)
Acupuncture

Methods
- Systematic review of 19 studies on the treatment of insomnia with acupuncture (Kalavapalli et al).
- Sample size: 18-288 individuals
- Participant ages: 15 to 91 years
- Duration of insomnia: 2 days to 19 years

Results
- 11/19 studies used subjective report of total sleep hours. All reported >80% (ranged 81.25-100%) as improved.
- Trials using objective measures (i.e. standardized questionnaires, wrist actigraphy, or overnight polysomnogram) reported significant improvement in SOL, TST, and SE.
Acupuncture Summary

- Limitations of studies
  - Patients with co-existing medical conditions
  - Considerable heterogeneity between comparison groups and outcomes measures

- The majority of studies using acupuncture have relied on subjective measures or have not had a placebo control, thus making interpretation of study findings difficult.

- Adverse effects can include: pain, increased risk of infection, risk of punctured organs

- Cost of treatment may be significant for some individuals.
  - Initial visit: $50-$125
  - Follow-up visit: $30-$80
Take Home Points

- **Benefit vs. Risk of CAM therapy**
  - Soft evidence
  - Relatively benign side effects, limited drug interactions
  - Lower risk of dependency?
  - More affordable

- **Integral role of pharmacists in CAM therapy**

- “To some it’s sushi, to others it’s bait”
References


-Question-