Treatment of Chronic Insomnia: From A to Zzz

Kathryn Lieber, MD
Clinical Instructor
Denver Health and Hospital
Division of General Internal Medicine
Department of Medicine
University of Colorado School of Medicine
Disclosures

• None
I've been having terrible insomnia lately.

Have you tried Powerpoints?
Why I Chose to Give This Talk?

Could Ambien increase your risk of death?
Objectives

• Brief review of diagnosis, causes and consequences of insomnia
• Efficacy of Cognitive Behavioral Therapy
• Efficacy and Risks of Pharmacotherapy:
  FDA approved drugs for insomnia
  Off-label prescriptions
  OTC/Herbal medications
Objectives

• Brief review of diagnosis, causes and consequences of insomnia
• Efficacy of Cognitive Behavioral Therapy
• Efficacy of Pharmacotherapy:
  FDA approved drugs for insomnia
  Off label prescriptions
  OTC/Herbal medications
• Risks of Pharmacotherapy
Definitions

- **Insomnia**: difficulty with the initiation, maintenance, duration or quality of sleep that results in the impairment of daytime functioning.
- **Research Criteria**:
  - Sleep Latency > 30 minutes
  - Sleep Efficiency < 85%
- **Duration of insomnia**:
  - Transient insomnia: < 1 week
  - Short-term insomnia: 1-4 weeks
  - Chronic insomnia: > 4 weeks
- **Prevalence of chronic insomnia** is 10%
Consequences of Insomnia

• Difficulty concentrating/cognitive impairment
• Higher risks of accidents
• Comorbid psychiatric conditions
• Comorbid medical conditions
• Increased health care utilization
• Decreased productivity, job absenteeism
Causes of Chronic Insomnia

- Medical disorders: CHF, COPD, asthma, GERD, cancer, chronic pain, hyperthyroidism, BPH, Parkinson’s, fibromyalgia.
- Primary sleep disorder: OSA, RLS, periodic limb movement disorder.
- Psychiatric disorders
- Sleep wake disorders: Irregular sleep–wake cycle, jet lag, shift work.
- Substance Abuse
- Medications: anticholinergics, antidepressants, antiepileptics, CNS stimulants, steroids, bronchodilators, diuretics, etc.
Objectives

• Brief review of diagnosis, causes and consequences of insomnia
• Efficacy of Cognitive Behavioral Therapy
• Efficacy and Risks of Pharmacotherapy:
  FDA approved drugs for insomnia
  Off label prescriptions
  OTC/Herbal medications
Cognitive Behavioral Therapy (CBT)

- Stimulus Control
- Sleep Hygiene
- Sleep Restriction
- Relaxation Therapy
- Cognitive Therapy

**FOR ALMOST ALL PATIENTS CBT SHOULD BE THE INITIAL TREATMENT**
Types of Cognitive Behavioral Therapy

Stimulus Control: behavior recommendations that reinforce the association of the bedroom with sleep and focus on a consistent sleep-wake schedule.

- Go to bed only when sleepy
- Use the bedroom only for sleeping and sex
- Get out of bed when unable to sleep >15 minutes
- Have a regular wake time regardless of sleep duration
- Avoid day time napping
Stimulus Control Therapy
Types of Cognitive Behavioral Therapy

Sleep Hygiene: recommendations about health practices and environmental factors that promote or interfere with sleep.

- Environmental disruptions (pets, snoring bed partner)
- Bedroom temperature
- Avoid alcohol, nicotine, caffeine
- Exercise
- Clock fixation
Sleep Hygiene

The most common cause of insomnia is a change in your daily routine. For example, traveling, change in work hours, disruption of other behaviors (eating, exercise, leisure, etc.), and relationship conflicts can all cause sleep problems. Paying attention to good sleep hygiene is the most important thing you can do to maintain good sleep.

Do:

1. Go to bed at the same time each day.
2. Get up from bed at the same time each day.
3. Get regular exercise each day, preferably in the morning. There is good evidence that regular exercise improves restful sleep. This includes stretching and aerobic exercise.
4. Get regular exposure to outdoor or bright lights, especially in the late afternoon.
5. Keep the temperature in your bedroom comfortable.
6. Keep the bedroom quiet when sleeping.
7. Keep the bedroom dark enough to facilitate sleep.
8. Use your bed only for sleep and sex.
9. Take medications as directed. It is helpful to take prescribed sleeping pills 1 hour before bedtime, so they are causing drowsiness when you lie down, or 10 hours before getting up, to avoid daytime drowsiness.
10. Use a relaxation exercise just before going to sleep.
   - Muscle relaxation, imagery, massage, warm bath, etc.
11. Keep your feet and hands warm. Wear warm socks and/or mittens or gloves to bed.

Don’t:

1. Exercise just before going to bed.
2. Engage in stimulating activity just before bed, such as playing a competitive game, watching an exciting program on television or movie, or having an important discussion with a loved one.
3. Have caffeine in the evening (coffee, many teas, chocolate, sodas, etc.).
4. Read or watch television in bed.
5. Use alcohol to help you sleep.
6. Go to bed too hungry or too full.
7. Take another person’s sleeping pills.
8. Take over-the-counter sleeping pills, without your doctor’s knowledge. Tolerance can develop rapidly with these medications. Diphenhydramine (an ingredient commonly found in over-the-counter sleep meds) can have serious side effects for elderly patients.
9. Take daytime naps.
10. Command yourself to go to sleep. This only makes your mind and body more alert.

If you lie in bed awake for more than 20-30 minutes, get up, go to a different room (or different part of the bedroom), participate in a quiet activity (e.g. non-excitable reading or television), and then return to bed when you feel sleepy. Do this as many times during the night as needed.

Estrategias para dormir bien durante la noche

¿Qué es el insomnio?
El insomnio es un problema común. Las personas con insomnio tienen dificultad ya sea para quedarse dormidas o para continuar durmiendo. La falta de sueño puede hacer que las personas con insomnio estén somnolientas durante el día. A veces el insomnio dura sólo por un corto tiempo. O bien, puede durar mucho tiempo. El insomnio puede afectar su trabajo, la escuela, su vida social y su salud. Algunos problemas de salud que pueden causar o empeorar el insomnio son la depresión, la ansiedad, las alergias y el dolor. El insomnio también puede ocurrir debido a que se tiene malos hábitos de sueño.

¿Cómo se trata el insomnio?
Los adultos con insomnio pueden utilizar medicamentos de venta libre o bien medicamentos recetados como ayuda para poder dormir. Pero los medicamentos de venta libre (difenhidramina /Benadryl/) pueden empeorar el insomnio en los niños. Lo mejor es buscar la causa del insomnio antes de comenzar el tratamiento con un medicamento. El mantener un diario de su sueño por una a dos semanas es una forma inteligente de comenzar. El seguimiento de las horas de sueño, del consumo de caféína y de alcohol, etcétera, puede proporcionar pistas. Un cambio en estos comportamientos podría ser todo lo que se necesita para ayudarle a dormir mejor.

Al mantener buenos hábitos de sueño (higiene de sueño), usted podría evitar tener que tomar un medicamento. En los niños, el mantener un horario de sueño regular y una rutina relajante puede ayudar.

Buenos hábitos de sueño

- Adhiérase a un horario regular para dormir -- incluso en los fines de semana.
- Haga ejercicio con regularidad -- evite el ejercicio en la noche.
- Acéstese sólo cuando tenga sueño.
- Olvide sus preocupaciones cuando usted se va a acostar.
- Antes de acostarse haga algo que la relaje y que sea agradable.
- Haga que su dormitorio sea un lugar tranquilo y confortable.
- Evite las comidas abundantes antes de acostarse.
- Use su habitación sólo para dormir y para actividad sexual.
- Si no se duerme en 15 o 20 minutos, levántese y vaya a otra habitación. Vuelva a la cama sólo cuando se sienta somnoliento.
- Mantenga el relaj fácil de la vista.
- No tome siestas durante el día. Si usted tiene que dormir la siesta, hágalo sólo por 30 minutos temprano en la tarde.
- Evite el consumo de alcohol, nicotina y cafeína.
- Evite el uso frecuente de sedantes.
- Pase tiempo al aire libre a la misma hora cada día.
- Haga que su farmacéutico revise sus medicamentos, para ver si alguno de ellos le impide dormir.
- Evite las luces brillantes de la televisión, del computador, de los juegos de video, etc. antes de acostarse.

Benefits of Exercise

- Improves sleep onset latency
- Improves sleep duration

Types of Cognitive Behavioral Therapy

Sleep Restriction Therapy: limits time in bed to actual sleep time, producing mild sleep deprivation resulting in more consolidated sleep.

- Reduce time in bed to estimated total sleeping time (minimum of 5 hours).
- Increase sleep window by 15 minutes every week when sleep efficiency is greater than 90%.
Types of Cognitive Behavioral Therapy

Relaxation Therapy

- Physical component: progressive muscle relaxation, biofeedback
- Mental component: imagery training and meditation
Types of Cognitive Behavioral Therapy

Cognitive Therapy: education to improve faulty beliefs about sleep

NOT GETTING THE RIGHT AMOUNT OF SLEEP EACH NIGHT CAN HAVE SERIOUS HEALTH RISKS AND CAN LEAVE LONG-LASTING EFFECTS ON YOUR BODY AND MIND.
Efficacy of Cognitive Behavioral Therapy

2 large meta-analysis conclude that compared to placebo CBT:

- Improves sleep onset latency by 30 minutes (60-70 minutes -> 35 minutes)
- Increases total sleep time by 30 minutes (6.0 -> 6.5 hrs)
- Improves the number and duration of awakenings
- Achieves a therapeutic response in 70-80% of patients, 40% achieve clinical remission
- Has sustained benefit over time
Feasibility Of CBT

• All patients should receive counseling about sleep hygiene and stimulus control.
• In studies, psychologists usually provide relaxation therapy and cognitive therapy.
• Given the prevalence of chronic insomnia, primary care physicians should familiarize themselves with CBT techniques.
• Individual therapy is slightly more effective than group therapy. However, group therapy or telephone interventions are probably more cost-effective.
• Abbreviated CBT (two 25 minute sessions) showed significant benefit, sustained at 2 months.
• Cost perceived as barrier, but because of CBT’s sustained effects is likely more cost-effective than pharmacotherapy.
Combination Therapy: Cognitive Behavioral Therapy and Medication

• Typically medication is tapered off after 6-8 weeks and CBT is continued.
• Evidence shows in short-term CBT alone, drug therapy alone and combination therapy all improve insomnia.
• Some studies have shown that at 10-24 months, improvements are maintained for cognitive behavioral therapy alone but not for combined therapy.
Changes in sleep-onset latency as measured by sleep diaries. CBT indicates cognitive behavior therapy.
Changes in sleep efficiency as measured by sleep diaries. CBT indicates cognitive behavior therapy.

**Figure Legend:**
Changes in sleep efficiency as measured by sleep diaries. CBT indicates cognitive behavior therapy.
Efficacy of CBT

• Decreases sleep latency by 30 minutes
• Increases total sleep time by 30 minutes
Objectives

• Brief review of diagnosis, causes and consequences of insomnia
• Efficacy of Cognitive Behavioral Therapy
• Efficacy and Risks of Pharmacotherapy:
  FDA approved drugs for insomnia
  Off label prescriptions
  OTC/Herbal medications
Pharmacotherapy for Insomnia

- Benzodiazepines*
- Non-benzodiazepine receptor agonists*
- Melatonin Receptor Agonists*
- Antidepressants
- Antihistamines
- Herbs and supplements

*FDA Approved for insomnia
Use of Sleep Aides

Benzodiazepines

- GABA (gamma aminobutyric acid) predominant inhibitory neurotransmitter in CNS
- Benzodiazepines act non-selectively at the α-subunit of the GABA receptor
- Non-benzodiazepines are more selective for the α1 subunit.

- Estazolam
- Quezepam
- Triazolam
- Flurazepam
- Temazepam

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
Efficacy of Benzodiazepines

- Decrease sleep latency (10 minutes)
- Decrease number of awakenings
- Increase in total sleep time (30 to 60 minutes)
Adverse Effects of Benzodiazepines

- Next day sedation
- Psychomotor impairment
- Cognitive impairment
- Anterograde amnesia
- Rebound insomnia
- Tolerance, abuse and dependence
Non-benzodiazepines

• Zolpidem (Ambien)
• Zaleplon (Sonata)
• Eszopiclone (Lunesta)
• Zolpidem ER (Ambien CR)
Efficacy of Non-benzodiazepines

- Decrease sleep onset latency by 18 minutes
- Improve sleep efficiency by 6%
- Increase total sleep time by 28 minutes

- Efficacy of non-benzodiazepines and traditional benzodiazepines are equivalent
## Non-benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Dose</th>
<th>Duration of Action</th>
<th>Half-life (hrs)</th>
<th>Approved Use</th>
<th>Long-term use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaleplon (Sonata)</td>
<td>5-10 mg</td>
<td>Ultra-short</td>
<td>1 hour</td>
<td>Sleep onset</td>
<td>No</td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>5-10 mg</td>
<td>Short</td>
<td>2-3 hours</td>
<td>Sleep Onset, Sleep maintenance</td>
<td>No</td>
</tr>
<tr>
<td>Zolpidem ER (Ambien CR)</td>
<td>6.25-12.5 mg</td>
<td>Intermediate</td>
<td>1.5-2.4 hours</td>
<td>Sleep onset, Sleep maintenance</td>
<td>Studied 6 months</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>2-3 mg</td>
<td>Intermediate</td>
<td>4 to 6 hours</td>
<td>Sleep onset, Sleep maintenance</td>
<td>Studied 12 months</td>
</tr>
</tbody>
</table>
Differences Among Non-benzodiazepine Hypnotics

- Zaleplon has the shortest half-life: can be used in middle of night - up to 4 hours before anticipated wake time.
- Zopli dendem has been approved for use up to 35 days, and Zolpidem ER has been studied up to 6 months.
- Eszoplicone is not limited to short term use: Efficacy studied up to 12 months.

No evidence of withdrawal upon discontinuation of treatment.

Long half life: need to be able to remain in bed for 8 hours.

Taking with or immediately after a high-fat meal has been shown to slow absorption and reduce the effect on sleep latency.

- Few comparison studies of effectiveness among the newer non-benzodiazepine hypnotics.
Adverse Effects of Non-benzodiazepines

• Common side effects:
  CNS: dizziness, headache, drowsiness
  GI: nausea, vomiting
• Complex sleep-related behaviors: sleep driving, making phone calls, sleep eating
• Minimal rebound insomnia
• Rare post-marketing reports of tolerance
Hypnotics and Mortality

- Some recent studies have reported increased mortality with hypnotics:

  *Hypnotics’ Association With Mortality or Cancer: A Matched Cohort Study*

  *Relationship of Zolpidem and Cancer Risk: A Taiwanese Population-Based Cohort Study*

  *Incidence of Infection May Be Increased Among Patients Taking Non-benzodiazepines: Meta-Analyses of Hypnotics and Infections: Eszopiclone, Ramelteon, Zaleplon, and Zolpidem*
Hypnotics’ Association With Mortality or Cancer: A Matched Cohort Study

- Geisinger Health System: large rural integrated health system in Pennsylvania.
- 250,000 outpatient visits a year.
- 12,465 patients were prescribed a hypnotic: 40% Zolpidem.
- Matched cases and controls by 12 classes of comorbidities. Data were adjusted for age, gender, smoking, body mass index, ethnicity, marital status, alcohol use and prior cancer.
- Results: Patients prescribed hypnotics had substantially higher hazards of dying compared to those who took no hypnotics.
Hypnotics’ Association With Mortality or Cancer

<table>
<thead>
<tr>
<th>Hypnotic</th>
<th>Deaths</th>
<th></th>
<th></th>
<th></th>
<th>Cancers</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hypnotic: doses/year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hypnotics, N=23676</td>
<td>&lt;0.001</td>
<td>3.60 (2.92 to 4.44)</td>
<td>&lt;0.001</td>
<td>0.86 (0.72 to 1.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4–18 pills/year, mean 8, N=3491</td>
<td>&lt;0.001</td>
<td>4.43 (3.67 to 5.36)</td>
<td>0.022</td>
<td>1.20 (1.03 to 1.40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–132 pills/year, mean 57, N=3548</td>
<td>&lt;0.001</td>
<td>5.32 (4.50 to 6.30)</td>
<td>&lt;0.001</td>
<td>1.35 (1.18 to 1.55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;132 pills/year, mean 469, N=3490</td>
<td>&lt;0.001</td>
<td></td>
<td>0.035</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem only: mg/year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No zolpidem or other hypnotics, N=23671</td>
<td>&lt;0.001</td>
<td>3.93 (2.98 to 5.17)</td>
<td>0.095</td>
<td>0.79 (0.60 to 1.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem 5–130 mg/year, mean 60, N=1453</td>
<td>&lt;0.001</td>
<td>4.54 (3.46 to 5.95)</td>
<td>0.585</td>
<td>1.07 (0.83 to 1.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem 130–800 mg/year, mean 360, N=1456</td>
<td>&lt;0.001</td>
<td>5.69 (4.58 to 7.07)</td>
<td>0.023</td>
<td>1.28 (1.03 to 1.59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem &gt;800 mg/year, mean 3600, N=1427</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temazepam only: mg/year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO temazepam or other hypnotics, N=23674</td>
<td>&lt;0.001</td>
<td>3.71 (2.55 to 5.38)</td>
<td>0.003</td>
<td>0.48 (0.30 to 0.77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temazepam 1–240 mg/year, mean 98, N=798</td>
<td>&lt;0.001</td>
<td>4.15 (2.88 to 5.99)</td>
<td>0.024</td>
<td>1.44 (1.05 to 1.98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temazepam 240–1640 mg/year, mean 683, N=613</td>
<td>&lt;0.001</td>
<td>6.56 (5.03 to 8.55)</td>
<td>&lt;0.001</td>
<td>1.99 (1.57 to 2.52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HRs associated with levels of hypnotic consumption from Cox proportional hazards survival analyses, controlled for age, gender, ethnicity, smoking status, body mass index, marital status and alcohol use and stratified by diagnoses in 12 classes of comorbidity. N: number of patients in each dose group for deaths. Restrictions of stratification produced small differences in N for the cancer analyses. p: probability that HR=1 from Cox proportional hazards models. For each drug, the top p level is for the overall contrast among dosage categories (including the no medication or reference category), and the lower p values are for the significance of each HR referenced to no hypnotic use. HR: hazard ratio for death or cancer (95% CI). Models for zolpidem and temazepam excluded patients receiving other hypnotics. See the supplemental files for additional HRs.

Any hypnotic 0-18 pills/year HR=3.60
Zolpidem 5-130mg/yr HR=3.93
>132 pills/year HR=5.32
>800 mg/year HR=5.69
Relationship of Zolpidem and Cancer Risk: A Taiwanese Population-Based Cohort Study

• Used data from National Health Insurance system in Taiwan.
• 14,950 patients who had received a first prescription of zolpidem over a 3 year period.
• Comparison patients matched by sex, age, and comorbidities.
• Results: risks of developing any cancer was greater in zolpidem users than nonusers. (HR 1.69, 95%CI, 1.55-1.82).

Hypnotics’ Association With Mortality or Cancer

• Cohort studies are observational; association does not indicate causality.

• Confounders may be present: i.e. depression (US study), tobacco use (Taiwanese study)

BUT, THESE MAY BE HELPFUL NUMBERS TO TELL YOUR PATIENTS...
Ramelteon

- Melatonin agonist
- Approved for **sleep onset** insomnia
- Original studies using polysomnography decreased sleep onset latency by 10-15 minutes and increased total sleep time by 10-15 minutes.
- Only approved sedative-hypnotic medication that is not a controlled/scheduled substance.
- Metabolized by the liver
Antidepressants

• Tricyclics, trazodone, mirtazapine may be effective for patients with insomnia who also have depression.

• No evidence that sedating antidepressants relieve insomnia in patients who do NOT have depression.
Doxepin

- Tricyclic antidepressant; usual starting dose for depression is 75mg-150mg.
- Low dose doxepin (1-10 mg) is highly selective H₁ antagonist and FDA approved for insomnia.
- Specifically studied in the elderly and effective in sleep maintenance insomnia.
- Does not appear to cause next day residual effects or rebound insomnia.
Table 2
Effect of doxepin 6 mg and placebo on sleep and global insomnia outcomes parameters at weeks 1 and 4.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th></th>
<th>Week 1</th>
<th></th>
<th>Week 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
<td>(SD)</td>
</tr>
<tr>
<td>sTST (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>293.5</td>
<td>(49.1)</td>
<td>316.7</td>
<td>(56.2)</td>
<td>336.4</td>
<td>(64.7)</td>
</tr>
<tr>
<td>DXP 6 mg</td>
<td>283.1</td>
<td>(50.0)</td>
<td>335.2**</td>
<td>(61.2)</td>
<td>346.1**</td>
<td>(66.4)</td>
</tr>
<tr>
<td>sWASO (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>112.0</td>
<td>(46.6)</td>
<td>97.4</td>
<td>(50.2)</td>
<td>78.9</td>
<td>(56.5)</td>
</tr>
<tr>
<td>DXP 6 mg</td>
<td>116.5</td>
<td>(49.1)</td>
<td>79.1***</td>
<td>(49.0)</td>
<td>66.5**</td>
<td>(43.9)</td>
</tr>
<tr>
<td>Sleep quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.7</td>
<td>(1.0)</td>
<td>-0.3</td>
<td>(1.0)</td>
<td>0.2</td>
<td>(1.1)</td>
</tr>
<tr>
<td>DXP 6 mg</td>
<td>-0.7</td>
<td>(0.9)</td>
<td>0.2***</td>
<td>(1.0)</td>
<td>0.4*</td>
<td>(1.0)</td>
</tr>
<tr>
<td>CGI-severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>4.8</td>
<td>(0.8)</td>
<td>4.3</td>
<td>(0.9)</td>
<td>3.9</td>
<td>(1.2)</td>
</tr>
<tr>
<td>DXP 6 mg</td>
<td>4.7</td>
<td>(0.8)</td>
<td>4.0*</td>
<td>(1.1)</td>
<td>3.7</td>
<td>(1.1)</td>
</tr>
<tr>
<td>CGI-improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>N/A</td>
<td>N/A</td>
<td>3.4</td>
<td>(0.9)</td>
<td>3.1</td>
<td>(1.1)</td>
</tr>
<tr>
<td>DXP 6 mg</td>
<td>N/A</td>
<td>N/A</td>
<td>3.0**</td>
<td>(1.1)</td>
<td>2.8</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Insomnia severity index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>17.5</td>
<td>(4.5)</td>
<td>15.8</td>
<td>(4.6)</td>
<td>14.0</td>
<td>(5.9)</td>
</tr>
<tr>
<td>DXP 6 mg</td>
<td>17.9</td>
<td>(4.3)</td>
<td>14.0***</td>
<td>(4.9)</td>
<td>12.5**</td>
<td>(5.5)</td>
</tr>
</tbody>
</table>

SD: standard deviation; DXP: doxepin; sWASO: subjective wake after sleep onset; sTST: subjective total sleep time.
* p < 0.05 versus placebo.
** p < 0.01.
*** p < 0.0001; sleep quality scale from -3 to 3; -3 = extremely poor to 3 = excel-
Doxepin

Trazodone

• Lack of evidence in non-depressed patients.
• 2005 review of 18 studies, found little evidence to support trazodone’s use.
• Trial of non-depressed patients who received placebo, zolpidem or trazodone for 2 weeks-
  After 1 week of therapy trazodone improved outcomes but after 2 weeks trazodone group did NOT differ from placebo.

Antihistamines

• Diphenhydramine and Doxylamine are NOT recommended.

• Proved to cause sedation, may cause subjective improvements in sleep, but worsen sleep quality.

• Associated with adverse effects: anticholinergic side effects, daytime sedation and cognitive impairment.
Herbal Products
Herbal Products

- Many herbal products have been promoted as sleep aides:
  - Melatonin
  - Valerian root
  - Lavender
  - Passion flower
  - Kava
  - St. John's wort
  - Glutamine
  - Niacin
  - L-tryptophan
Melatonin

2 Meta-Analysis:

**Effects of Exogenous Melatonin on Sleep: A Meta-Analysis**
Reduced sleep onset latency by 4.0 minutes
Increased sleep efficiency by 2.2%
Increased total sleep duration by 12.8 minutes
Conclusion: “The present meta-analysis implies that exogenous melatonin might have some use in treating insomnia.”

**The Efficacy and Safety of Exogenous Melatonin for Primary Sleep Disorders: A Meta-Analysis**
Decreased sleep onset latency by 11.7 minutes: “Although the result was statistically significant, the effect appears to be clinically unimportant.”
Sleep efficiency favored melatonin (2.5% increase) but not statistically significant.

Effects of Exogenous Melatonin on Sleep: A Meta-analysis. Brzezinski, A. Sleep medicine reviews. 9 (1) 1087-0792. 02/2005
Melatonin

- Many review articles on insomnia treatment do not recommend melatonin.
- Two meta-analysis’ show it does appear to decrease sleep latency.
- Recommend dose 1-3 mg 1 hr before bedtime.
- Appears to be safe (with exception of use with calcium channel blockers).
- Better data for patients with Delayed Sleep Phase Syndrome, jet lag and shift-work disorder.
- Potential use as placebo?
Valerian

• Studied in several randomized, placebo-controlled studies, doses from 400-900 mg.

• Meta-analysis in *Sleep Medicine*:
  Decreased objective sleep latency by < 1 minute
  Patients report subjective improvement.

Alcohol

• Commonly self-prescribed.
• May decreases the time required to fall asleep, at least in the short time.
• Promotes sleep disturbances later in the night and promotes sleep apnea.
On the Horizon?...Suvorexant

- Suvorexant works by blocking orexin.
- Phase III trials completed and presented at Sleep2012 conference.
# Treatment Effectiveness

<table>
<thead>
<tr>
<th></th>
<th>CBT</th>
<th>Exercise</th>
<th>Benzos</th>
<th>Non-benzos</th>
<th>Ramelteon</th>
<th>Doxepin</th>
<th>Melatonin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep Onset Latency</strong> (Decrease in minutes)</td>
<td>30 minutes</td>
<td>14</td>
<td>10</td>
<td>18</td>
<td>10-15</td>
<td>12</td>
<td>4-11</td>
</tr>
<tr>
<td><strong>Total Sleep Time</strong> (Increase in minutes)</td>
<td>30 minutes</td>
<td>48</td>
<td>30-60</td>
<td>28</td>
<td>10-15</td>
<td>12</td>
<td>0-12</td>
</tr>
</tbody>
</table>
My Recommendations

✓ Cognitive Behavioral Therapy (CBT) should be first-line treatment for almost all patients with insomnia.
✓ CBT is the most effective, least risky, and most sustainable treatment for insomnia.
✓ Emphasize the benefits of exercise.
✓ Prescribe non-benzodiazepines for insomnia recalcitrant to CBT. Prescribe for shortest duration possible, and counsel patients on potential side effects and possible association with increased mortality.
✓ Eszopiclone has the best data for long-term treatment of insomnia, but is also the non-benzodiazepine with the longest half-life.
✓ Do not recommend antidepressants if the patient does not have depression.
✓ Advise against antihistamines.
✓ Consider the use of melatonin.
✓ Recognize the power of the placebo effect in insomnia studies.
✓ Remember there is no data that treating insomnia improves the negative consequences of insomnia.
References

• Comparative Tolerability of Newer Agents for Insomnia. Zammit, Gary. Drug Safety; 2009, Vol. 32 Issue 9, p735-748
• Efficacy and Safety of Doxepin 1 mg and 3 mg in a 12-week Sleep Laboratory and Outpatient Trial of Elderly Subjects with Chronic Primary Insomnia. Krystal AD et al. Sleep. 33(11):1553-61, 2010 Nov
• Efficacy and Safety of Doxepin 6 mg in a Four-week Outpatient Trial of elderly Adults With Chronic Primary Insomnia. Lankford A et al. Sleep Medicine. 13(2):133-8, 2012 Feb.
• Nonpharmacologic Management of Chronic Insomnia. Harsora P and Kennmann J. American Family Physician. Volume 79, Number 2, 125-130
• Chronic Insomnia. Morin C and Benca R. Lancet 2012 379:1129-1141
References continued

- The Assessment and Management of Insomnia in Primary Care. Falloon K et al. BMJ. 2011 May 27;342:
- JIM. G The Efficacy and Safety of Drug Treatments for Chronic Insomnia in Adults: A Meta-analysis of RCTs. Buscemi N et al. 2007 Sep;22(9):1335-50
- Effects of exogenous melatonin on sleep: a meta-analysis. Brzezinski, A. Sleep medicine reviews. 9 (1) 1087-0792. 02/2005
You may now wake up for QUESTIONS