Psychopharmacology of Sleep Disorders

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Disclosure Information

Type of Affiliation

• Consultant/Honoraria

• Research Grant

Commercial Entity

Advance Medical
Avadel
Disc Medicine
Eisai
Emalex
Noctrix
UpToDate

Luitpold/American Regent
Merck
NIDA
RLS Foundation
Transdiagnostic and causally bidirectional

Sleep Disorders
- Insomnia
- Hypersomnia
- RLS
- Obstructive Sleep Apnea
- Nightmares

Psychiatry
- Major Depression
- Bipolar Disorder
- PTSD
- Suicide
- Substance Use Disorder
- Alzheimer’s Disease

How to Identify and Fix Sleep Problems
Better Sleep, Better Mental Health

John W. Winkelman, MD, PhD

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Sleep disorders

- **Insomnias**
  - Insomnia, psychiatric/medical disorders, RLS, medications
- **Hypersomnias**
  - Sleep apnea, medications, Periodic leg movements of sleep
- **Parasomnias**
  - Sleepwalking, sleep terrors, REM sleep behavior disorder
- **Circadian rhythm disorders**
  - Shift work sleep disorder, Delayed sleep phase disorder
DSM-5 Insomnia disorder

• Dissatisfaction with sleep quality or quantity associated with (at least one of):
  • difficulty initiating sleep
  • difficulty maintaining sleep
  • early morning awakening

• Distress or dysfunction related to sleep disturbance

• Minimum of 3x/wk for 3 months

• The insomnia does not co-occur with another sleep disorder

• The insomnia is not *explained* by coexisting mental disorders or medical conditions
Most sleep problems are transient but 25-30% last > 1 year

Roth et al, Biol Psych 2006
Medication treatment of sleep disturbance is warranted in patients with acute insomnia

- Acute insomnia often has an identifiable precipitant
- Difficulty falling or staying asleep, or early AM awakening
- Have distress or dysfunction as a result of sleep disturbance
- No better explanation for sleep disturbance than current precipitant

- Assess risk of side effects with medication
- Evaluate risk of misuse/abuse/diversion
- Check PMP for use of other sedatives
Chronic Insomnia Requires a Thorough Evaluation

Symptoms → Differential Diagnosis

Treatment ← Diagnosis
Sleep quality is only as strong as the weakest link and insomniacs often have many sleep-related issues.

All contributing factors must be treated to achieve maximum benefit.
Discuss and **prioritize** treatment goals with the patient

1. Primary Goals:
   - Improvement in sleep quality and/or time.
   - Improvement of insomnia-related daytime impairments such as improvement of energy, attention or memory difficulties, cognitive dysfunction, fatigue, or somatic symptoms.

2. Other Goals:
   - Improvement in an insomnia symptom (SOL, WASO, # awakenings) such as:
     - SOL <30 minutes and/or
     - WASO <30 minutes and/or
     - Decreased frequency of awakenings or other sleep complaints
     - TST >6 hours and/or sleep efficiency >80% to 85%.
   - Formation of a positive and clear association between the bed and sleeping
   - Improvement in sleep related psychological distress

Schutte-Rodin et al, JCSM, 2008
Our understanding of the regulation of sleep informs insomnia treatment approaches

Two processes control sleep timing, quality and quantity

1. Homeostatic Drive
   - Increases with the duration of waking and dissipates with sleep

2. Circadian Rhythms
   - Confines sleep and waking to different phases of the 24-hour day
   - Entrained to the light-dark cycle
   - Sleep-independent
Differential diagnosis of chronic insomnia

- Primary psychiatric disorders
- Medications
- Substances
- Medical disorders
- Restless Legs Syndrome (RLS)
- Sleep schedule disorders
- Obstructive sleep apnea
Indications for polysomnography

- Suspicion of sleep apnea (loud snoring *PLUS one of the following*):
  - daytime sleepiness
  - witnessed apneas
  - refractory hypertension

- Abnormal behaviors or movements during sleep
- Unexplained excessive daytime sleepiness
- Refractory sleep complaints, particularly repetitive brief awakenings
Common cognitive and behavioral issues which can produce/worsen insomnia

- Inconsistent bedtimes and wake times
- “Dozing” in evening before bed
- Excessive time in bed
- Sleep-related anxiety ("insomnia phobia")
- Unrealistic expectations of total sleep time, sleep onset and number of awakenings
- Clock watching
- Use of electronics in bedroom
- Inappropriate attributions of daytime issues to sleep
Psychiatric disorders are present in only 30-40% of those with insomnia.
Independent treatment of insomnia in MDD improves depression treatment outcome
Sleep disturbance is the most common persistent symptom in treated MDD.

**25% had treatment-emergent onset of nocturnal awakenings (Nierenberg et al, 2012)**

MDD = Major depressive disorder.
PTSD is a disorder with an essential difficulty maintaining states of decreased vigilance.

PTSD will therefore nearly always interfere with sleep.

Specific questions as to the circumstances of traumatic episodes (e.g., night, bedroom) may shed light on sleep disturbance.

Treatments:
- Education as to relationship of PTSD to sleep disturbance
- Safety of sleep environment
- Judicious use of hypnotics
- Prazosin or image rehearsal therapy for nightmares
INSOMNIA RELATED TO MEDICATIONS

• Antidepressants
• Stimulants
• Steroids, bronchodilators
• Decongestants
Stimulant pharmacokinetics are not kind to sleep
Insomnia in the elderly is not related to age, but to medical illness

- **Cardiac**: angina, PND
- **Pulmonary**: COPD, coughing
- **GI**: Nocturnal reflux
- **Musculoskeletal pain**
- **Endocrine**: Hypo/hyperthyroidism, diabetes, menopause
- **Neurologic**: Dementia, Parkinson’s, CVA, migraine
- **Urinary**: Nocturia, renal failure
Diagnosis and Treatment of Restless Legs Syndrome

- URGE diagnostic criteria
- Modify reversible causes
  - Iron Deficiency (keep Ferritin > 50)
  - Medication-Induced (SRIs, DA antagonists, antihistamines)
- Pharmacologic approaches
  - Dopaminergic agonists (pramipexole, ropinirole, rotigotine patch) but watch for iatrogenic worsening of RLS ("augmentation")
  - Alpha 2 delta ligands (gabapentin, pregabalin)
  - Opioids (oxycodone, methadone)
SLEEP SCHEDULE DISORDERS

• Delayed Sleep Phase Syndrome
  • Most common in adolescents
  • Initial insomnia and difficulty awakening in AM
  • Daytime sleepiness

• Advanced Sleep Phase Syndrome
  • Most common in the elderly
  • Early AM awakening
OSA is common in those with psychiatric illness
Physical exam (kind of) predicts likelihood of sleep apnea
OSA treatments

Positive Airway Pressure (PAP)

Auto-PAP is allowing both diagnostic and titration to be performed in the home (no sleep lab necessary)

Weight loss, upper airway surgery, positional treatment
Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Devan Kansagara, MD, MCR; Mary Ann Forciea, MD; Molly Cooke, MD; and Thomas D. Denberg, MD, PhD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the management of chronic insomnia disorder in adults.

Methods: This guideline is based on a systematic review of randomized, controlled trials published in English from 2004 through September 2015. Evaluated outcomes included global outcomes assessed by questionnaires, patient-reported sleep outcomes, and harms. The target audience for this guideline includes all clinicians, and the target patient population includes adults with chronic insomnia disorder. This guideline grades the evidence and recommendations by using the ACP grading system, which is based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Recommendation 1: ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)

Recommendation 2: ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)

For author affiliations, see end of text.
This article was published at www.annals.org on 3 May 2016.
### Table 2. Components of Cognitive Behavioral Therapy for Insomnia.

<table>
<thead>
<tr>
<th>Component</th>
<th>Intended Effect</th>
<th>Specific Directions for Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep restriction</td>
<td>Increase sleep drive and stabilize circadian rhythm</td>
<td>Reduce time in bed to perceived total sleep time (not less than 5–6 hours), choose specific hours on the basis of personal preference and circadian timing, increase time in bed gradually as sleep efficiency improves</td>
</tr>
<tr>
<td>Stimulus control</td>
<td>Reduce arousal in sleep environment and promote the association of bed and sleep</td>
<td>Attempt to sleep when sleepy, get out of bed when awake and anxious at night, use the bed only for sleep or sexual activity (e.g., no watching TV in bed)</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Restructure maladaptive beliefs regarding daytime and health consequences of insomnia</td>
<td>Maintain reasonable expectations about sleep; review previous insomnia experiences, challenging perceived catastrophic consequences</td>
</tr>
<tr>
<td>Relaxation therapy</td>
<td>Reduce physical and psychological arousal in sleep environment</td>
<td>Practice progressive muscle relaxation, breathing exercises, or meditation</td>
</tr>
<tr>
<td>Sleep hygiene</td>
<td>Reduce behaviors that interfere with sleep drive or increase arousal</td>
<td>Limit caffeine and alcohol, keep bedroom dark and quiet, avoid daytime or evening napping, increase exercise (not close to bedtime), remove bedroom clock from sight</td>
</tr>
</tbody>
</table>

Online CBT-I programs do work
CBT-I (online) effective for sleep latency, wake after sleep onset, but not for total sleep time

Ritterband et al, JAMA Psychiatry, 2017
CBT-I non-response and medication initiation

• Ritterband (SHUTi, 2017): non-responder rate: 50% at 9 weeks, 40% at 6 months, and 30% at 1 year follow-up

• These are individuals for whom it is appropriate to consider a medication trial

• Whether to start medication depends on the severity of the persistent insomnia, comorbidities, and previous response to hypnotics
“A story? Honey, wouldn't you rather a mild sedative?”
The complex neurochemistry of sleep provides many treatment options.
Pharmacologic Treatments for Insomnia

- Benzodiazepine receptor agonists (BzRAs)
- Melatonin agonists
- Orexin antagonists
- Sedating antidepressants
- Anticonvulsants
- Dopaminergic antagonists (eg antipsychotics)
- Miscellaneous (eg prazosin, clonidine, hydroxyzine)
## Benzodiazepine-Receptor Agonists (BzRA) Commonly Used as Hypnotics

<table>
<thead>
<tr>
<th>Agent (brand name)</th>
<th>Dose range</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.25 -1.0 mg</td>
<td>40 hr</td>
</tr>
<tr>
<td>Temazepam (Restoril)*</td>
<td>7.5-30 mg</td>
<td>4-18 hr</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>0.5-2.0 mg</td>
<td>10-20 hr</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>10-30 mg</td>
<td>5-10 hr</td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)*</td>
<td>1-3 mg</td>
<td>5.5-8 hr</td>
</tr>
<tr>
<td>Triazolam (Halcion)*</td>
<td>0.125-0.25 mg</td>
<td>2-3 hr</td>
</tr>
<tr>
<td>Zolpidem (Ambien)*</td>
<td>3.75-12.5 mg</td>
<td>2-3 hr (CR extends duration of action)</td>
</tr>
<tr>
<td>Zaleplon (Sonata)*</td>
<td>5-10 mg</td>
<td>1-2 hr</td>
</tr>
</tbody>
</table>

*FDA approved for insomnia.
Response with BZRAs is common but remission is only ~ 50% in clinic patients.

Figure 3—Response and remission rates, stratified by medical/psychiatric comorbidity. Med = medical; Pscy = psychiatric; Com = comorbidity. *p < .05.

Pillai et al 2017
“Are sleeping pills addictive?”

“Substance use disorders occur when their recurrent use causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home.”- DSM 5

• Tolerance
• Physiological dependence
• Psychological dependence
• Non-medical diversion
Misuse of sedative-hypnotics is age-related

Misuse: “using the medication in any way a doctor did not direct you to use them...including: Using it without a prescription of your own; Using it in greater amounts, more often, or longer than you were told to take it; Using it in any other way a doctor did not direct you to use it.”

Table 1
Prevalence of lifetime and past year sedative/tranquilizer use and lifetime, past year and past 30-day misuse by age group.

<table>
<thead>
<tr>
<th></th>
<th>12–17 years (adolescents) (a)</th>
<th>18–25 years (young adults) (b)</th>
<th>26–34 years (c)</th>
<th>35–49 years (d)</th>
<th>50–64 years (e)</th>
<th>65 and older (f)</th>
<th>Post hoc Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>27,857</td>
<td>38,213</td>
<td>17,835</td>
<td>22,550</td>
<td>10,398</td>
<td>7210</td>
<td>a &lt; b &lt; c &lt; f &lt; d, e</td>
</tr>
<tr>
<td>Lifetime use</td>
<td>2229</td>
<td>5398</td>
<td>4871</td>
<td>7395</td>
<td>3901</td>
<td>2549</td>
<td>f &lt; a &lt; e &lt; d &lt; b &lt; c</td>
</tr>
<tr>
<td>Weighted % of population (95% CI)</td>
<td>7.9  (7.5–8.3)</td>
<td>19.6  (18.3–19.7)</td>
<td>27.3 (26.4–28.2)</td>
<td>31.6 (30.8–32.3)</td>
<td>37.2 (36.1–38.4)</td>
<td>35.3 (34.0–36.6)</td>
<td>f &lt; a &lt; e &lt; d &lt; b &lt; c</td>
</tr>
<tr>
<td>Lifetime misuse</td>
<td>638</td>
<td>2143</td>
<td>1385</td>
<td>1279</td>
<td>549</td>
<td>167</td>
<td>f &lt; e &lt; d &lt; a &lt; b, c</td>
</tr>
<tr>
<td>Weighted % of population (95% CI)</td>
<td>2.3  (2.1–2.5)</td>
<td>7.6  (7.4–8.3)</td>
<td>8.1 (7.6–8.6)</td>
<td>5.4 (5.1–5.8)</td>
<td>5.3 (4.8–5.9)</td>
<td>2.2 (1.8–2.7)</td>
<td>f &lt; e &lt; d &lt; a &lt; b, c</td>
</tr>
<tr>
<td>Weighted % of those with lifetime use (95% CI)</td>
<td>29.6  (27.3–31.9)</td>
<td>41.3  (39.5–43.2)</td>
<td>29.6 (27.9–31.3)</td>
<td>17.2 (16.0–18.4)</td>
<td>14.3 (13.0–15.8)</td>
<td>6.3 (5.2–7.6)</td>
<td>f &lt; e &lt; d &lt; a &lt; b, c</td>
</tr>
<tr>
<td>Past year use</td>
<td>1682</td>
<td>3816</td>
<td>2943</td>
<td>4445</td>
<td>2413</td>
<td>1574</td>
<td>a &lt; b &lt; c&lt;f, e &lt; c</td>
</tr>
<tr>
<td>Weighted % of population (95% CI)</td>
<td>6.0  (5.6–6.4)</td>
<td>13.5  (13.0–14.0)</td>
<td>16.6 (15.9–17.3)</td>
<td>18.8 (18.2–19.4)</td>
<td>22.8 (21.8–23.8)</td>
<td>21.9 (20.7–23.1)</td>
<td>f &lt; e &lt; d &lt; a &lt; b, c</td>
</tr>
<tr>
<td>Past year misuse</td>
<td>523</td>
<td>1543</td>
<td>687</td>
<td>541</td>
<td>197</td>
<td>65</td>
<td>f &lt; a &lt; e &lt; d &lt; b, c</td>
</tr>
<tr>
<td>Weighted % of population (95% CI)</td>
<td>1.9  (1.7–2.1)</td>
<td>5.6  (5.4–6.2)</td>
<td>4.0 (3.7–4.4)</td>
<td>2.4 (2.1–2.6)</td>
<td>1.9 (1.6–2.3)</td>
<td>0.9 (0.7–1.2)</td>
<td>b &lt; a, c &lt; d &lt; e &lt; f</td>
</tr>
<tr>
<td>Weighted % of those with past-year use (95% CI)</td>
<td>31.4  (28.4–34.6)</td>
<td>42.8  (40.6–45.2)</td>
<td>24.2 (22.5–26.0)</td>
<td>12.6 (11.5–13.8)</td>
<td>8.4 (7.0–10.0)</td>
<td>4.2 (3.1–5.5)</td>
<td>f &lt; a&lt;; a &lt; b&lt;d; d &lt; e &lt; f</td>
</tr>
<tr>
<td>Past 30-day misuse</td>
<td>171</td>
<td>471</td>
<td>232</td>
<td>205</td>
<td>62</td>
<td>18</td>
<td>f &lt; a&lt;; a &lt; b&lt;d; d &lt; e &lt; f</td>
</tr>
<tr>
<td>Weighted % of population (95% CI)</td>
<td>0.7  (0.5–0.8)</td>
<td>1.8  (1.5–2.0)</td>
<td>1.4 (1.2–1.6)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.5 (0.4–0.7)</td>
<td>0.3 (0.1–0.6)</td>
<td>f &lt; a; a &lt; b; d, e &lt; b, c</td>
</tr>
</tbody>
</table>

Source: NSDUH, 2015–16 cohorts.
Notes: Post hoc comparisons controlled for race/ethnicity and sex and were only noted when the p-value was at or below a Bonferroni-corrected value of 0.00333 (0.05/15 = 0.00333). Unweighted samples and weighted percentages are provided, with 95% confidence intervals following the weighted percentages.
Are benzodiazepines dangerous?

- Complex sleep-related disorders
- Dementia
- Mortality
Raiding the Refrigerator, but Still Asleep

Sleeping pills are as dangerous as smoking a packet of cigarettes A DAY, expert claims

- A worrying body of evidence is emerging over the dangers of sleeping tablets
- Recent studies have seen them linked to cancer, falls and even heart attacks

Ask Well: Do Sleeping Pills Induce Restorative Sleep?

Is sleep induced by a benzodiazepine counted as restorative sleep?

Researchers hate to admit it, but they don’t know enough about sleep to answer this question. Their best guess, several experts said, is that sleep is sleep.

Dr. John Weyl Winkelman, a sleep disorders expert at Massachusetts General Hospital and Harvard Medical School, said many people feel better the next day when they take sleeping pills, but he cannot scientifically explain why this is so.

Lowell - In what could prove to be a precedent-setting case, an Andover attorney was cleared yesterday of a charge of motor-vehicle homicide because he may have been "sleep driving" while under the influence of Ambien.

Ki Yong O struck and killed 43-year-old Anthony Raucci on June 30, 2006, as the Methuen man was changing a tire in the breakdown lane on Interstate-93 in Tewksbury.

Lowell Superior Court Judge Kenneth Fishman accepted expert testimony that O may have been "sleep driving" when he hit and killed Raucci.

As Fishman announced that O was innocent of motor-vehicle homicide and leaving the scene accident after property damage, Raucci's widow, Elena Raucci, sobbed uncontrollably in the the courtroom.

She declined to comment after the verdict.

O merely nodded his head and left the courtroom without comment -- his career, his livelihood, his freedom intact.

In announcing his verdict following the jury-waived trial, Fishman said the only disputable element of the case, which centered on the use of prescription drugs, is whether O knew of the side effects of the powerful sleeping pill.
The Current Status of BzRA Risks in the Treatment of Insomnia

- Motor vehicle accidents in elderly: long T$_{1/2}$ agents
- Hip fractures in elderly: long T$_{1/2}$ agents?
- Anterograde amnesia: T$_{1/2}$ dependent
- Rebound insomnia: depends upon dose, duration of use, and speed of taper

Benzodiazepines do increase risk for dementia

---

Table 3 | Risk of Alzheimer’s disease associated with benzodiazepine use (variables assessed five to up to 10 years before diagnosis) in people with Alzheimer’s disease (cases) and controls

<table>
<thead>
<tr>
<th></th>
<th>No (%) of cases (n=1796)</th>
<th>No (%) of controls (n=7184)</th>
<th>Univariable odds ratio (95% CI)*</th>
<th>Multivariable odds ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Model 1‡</td>
</tr>
<tr>
<td>Benzodiazepine ever use:</td>
<td></td>
<td></td>
<td></td>
<td>Model 2‡</td>
</tr>
<tr>
<td>Non-users</td>
<td>902 (50.2)</td>
<td>4311 (60.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Users</td>
<td>894 (49.8)</td>
<td>2873 (40.0)</td>
<td>1.52 (1.37 to 1.69)</td>
<td>1.51 (1.36 to 1.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.43 (1.28 to 1.60)</td>
</tr>
<tr>
<td>Benzodiazepine density exposure (No of prescribed daily doses):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-users</td>
<td>902 (50.2)</td>
<td>4311 (60.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1-90</td>
<td>234 (13.0)</td>
<td>1051 (14.6)</td>
<td>1.08 (0.92 to 1.27)</td>
<td>1.09 (0.92 to 1.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.05 (0.89 to 1.24)</td>
</tr>
<tr>
<td>91-180</td>
<td>70 (3.9)</td>
<td>257 (3.6)</td>
<td>1.33 (1.01 to 1.75)</td>
<td>1.32 (1.01 to 1.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.28 (0.97 to 1.69)</td>
</tr>
<tr>
<td>&gt;180</td>
<td>590 (32.9)</td>
<td>1565 (21.8)</td>
<td>1.85 (1.63 to 2.09)</td>
<td>1.84 (1.62 to 2.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.74 (1.53 to 1.98)</td>
</tr>
<tr>
<td>Benzodiazepine elimination half life:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-users</td>
<td>902 (50.2)</td>
<td>4311 (60.0)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Short half life (&lt;20 h)</td>
<td>585 (32.6)</td>
<td>1996 (27.8)</td>
<td>1.43 (1.27 to 1.61)</td>
<td>1.43 (1.27 to 1.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.37 (1.21 to 1.55)</td>
</tr>
<tr>
<td>Long half life (≥20 h)</td>
<td>309 (17.2)</td>
<td>877 (12.2)</td>
<td>1.72 (1.48 to 1.99)</td>
<td>1.70 (1.48 to 1.98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.59 (1.36 to 1.85)</td>
</tr>
</tbody>
</table>

*Matched for age, sex, and follow-up length.
†Adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).
‡Further adjusted for anxiety, depression, and insomnia diagnosis.

Billioti de Gage et al, BMJ, 2014
Benzodiazepines do not increase risk for dementia

Gray et al, BMJ, 2016
Do benzodiazepines increase mortality risk?

Patorno et al, BMJ, 2017
Melatonin leads to small benefits for insomnia

Figure 1. Efficacy of Melatonin in Reducing Sleep Latency. Forest plot depicting reduction of sleep latency in melatonin compared to placebo. Meta-analysis demonstrated a significant benefit of melatonin in reducing sleep latency. WMD = weighted mean difference; CI = confidence interval.

Figure 2. Efficacy of Melatonin in Increasing Total Sleep Time. Forest plot depicting change in total sleep time with melatonin compared to placebo treatment. Meta-analysis demonstrated a significant benefit of melatonin in increasing total sleep time. WMD = weighted mean difference.

Figure 3. Effect of Melatonin on Sleep quality. Forest plot depicts sleep quality with melatonin compared to placebo. Meta-analysis demonstrated a significant benefit of melatonin in improving sleep quality. SMID = standardized mean difference; CI = confidence interval.
Orexin antagonists in the treatment of insomnia

-Suvorexant 10-20 mg, Lemborexant 5-10 mg

- Advantages: little abuse liability, 1-year efficacy data, few side effects
- Disadvantages: prior authorization
Antidepressants in the treatment of insomnia

- Mirtazapine (15-30 mg), Trazodone (25-100 mg), Amitriptyline and Doxepin (10-50 mg)

- Advantages: little abuse liability
- Disadvantages: probably not as effective as BzRAs, daytime sedation, weight gain, anticholinergic side effects
Anticholinergic medications and incident dementia

Gray et al, JAMA Int Med, 2015

“We found that among the heaviest users, people who had past heavy use had a similar dementia risk as those with recent or continued heavy use. This suggests that the risk for dementia with anticholinergic use may persist despite discontinuation.”

<table>
<thead>
<tr>
<th>TSDD $^b$</th>
<th>Follow-up time (person-years)</th>
<th>Number of Events</th>
<th>Unadjusted $^{cd}$</th>
<th>Adjusted $^{de}$</th>
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<tr>
<td>Dementia</td>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<td>5618</td>
<td>136</td>
<td>1.00</td>
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<td>203</td>
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<td>5051</td>
<td>172</td>
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<td>2626</td>
<td>102</td>
<td>1.39</td>
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<td>&gt;1095</td>
<td>4022</td>
<td>184</td>
<td>1.77</td>
<td>1.40-2.23</td>
</tr>
</tbody>
</table>

| Alzheimer’s Disease |                               |                  | HR     | 95% CI   | HR     | 95% CI   |
|---------------------|-------------------------------|------------------|--------------------|------------------|
| 0                   | 5618                          | 112              | 1.00   | Reference | 1.00   | Reference |
| 1-90                | 7704                          | 168              | 0.96   | 0.75-1.24 | 0.95   | 0.74-1.23 |
| 91-365              | 5051                          | 128              | 1.21   | 0.93-1.58 | 1.15   | 0.88-1.51 |
| 366-1095            | 2626                          | 83               | 1.38   | 1.03-1.85 | 1.30   | 0.96-1.76 |
| >1095               | 4022                          | 146              | 1.73   | 1.34-2.24 | 1.63   | 1.24-2.14 |

TSDD Total Standardized Daily Dose; HR Hazard Ratio; CI Confidence Interval; ACT Adult Changes in Thought

$^a$ Observations with missing adjustment variables are excluded from the model (n=115; 3.3%).

$^b$ TSDD example; the minimum effective daily dose for oxybutynin is 5 mg daily ($=1$ TSDD); a person would fall into the following TSDD category if they were using 5 mg daily for 45 days (TSDD 1-90); 5 mg daily for 180 days (TSDD 91-365); 5 mg daily for 720 days (TSDD 366-1095); 5 mg daily for 4 years (TSDD>1095)

$^c$ Age adjustment via the time-axis.

$^d$ Test for trend P value<0.001 for an association between exposure categories and each outcome

$^e$ Adjusted for ACT cohort, age (via the time-axis), age at ACT study entry, sex, education, body mass index, current smoking, regular exercise, self-rated health, hypertension, diabetes, stroke, coronary heart disease, Parkinson’s disease, history of depressive symptoms, and current benzodiazepine use.
Atypical antipsychotics in the treatment of insomnia

*Quetiapine (25-100 mg)*

- Advantages: anxiolytic, mood stabilizing in bipolar disorder, little abuse liability
- Disadvantages: less effective than BzRAs, daytime sedation, weight gain, risks of extrapyramidal symptoms and glucose + lipid abnormalities
Anticonvulsants in the treatment of insomnia

*Gabapentin (300-900 QHS or split dosing)*

- Advantages: mildly analgesic, anxiolytic
- Disadvantages: less effective than BzRAs, cognitive impairment, daytime sedation, dizziness, weight gain, concerns re abuse
Issues with non-BzRA hypnotics in the treatment of insomnia (eg antidepressants, anticonvulsants, antipsychotics)

- Paucity of short-term efficacy data
- Absence of long-term efficacy data
- Assumptions of lack of tolerance and rebound insomnia are unsubstantiated
- Anecdotally less effective hypnotics than BzRAs
- May have deleterious side effects
Severe primary insomniacs on BZRA x 19 yrs
At 7 weeks:
  - Small improvements in sleep latency, WASO; large reductions in total sleep time
  - Substantial improvements in ISI
  - Medication tapering + CBT modest superiority to either alone
Taper and discontinuation of hypnotics in insomniacs with persistent poor sleep did not produce worsened sleep.

CBT was not of particular benefit in enhancing sleep endpoints beyond supervised medication taper.
Summary

• Insomnia is common, both acute and chronic
• Differential diagnosis and assessment of chronic insomnia is essential to treatment success
• Prioritize goals of therapy and reassess treatment efficacy regularly
• CBT-I is first line therapy of chronic insomnia
• Many medication options are available if CBT-I is not effective
• Medication choice is a shared decision between provider and patient based on comparative risks of insomnia and medications, rather than on shaming
• Medication tapering should be discussed with patients on long-term therapy, particularly in older patients and those with persistent insomnia
Sleep disorders

- Insomnias
  - Insomnia, psychiatric/medical disorders, RLS, medications
- Hypersomnias
  - Sleep apnea, medications, Periodic leg movements of sleep
- Parasomnias (4%)
  - Sleepwalking, sleep terrors, REM sleep behavior disorder
- Circadian rhythm disorders
  - Shift work sleep disorder, Delayed sleep phase disorder
Differential diagnosis of hypersomnia

• “Tired”:
  • excessive daytime sleepiness (EDS)
  • fatigue
  • apathy

• *If* EDS:
  • inadequate sleep time
  • impaired sleep quality
  • excessive sleep drive
Epworth Sleepiness Scale

“how likely to dose off or fall asleep”
0= not likely at all; 3= very likely
(range of scale 0-24, with abnormal > 10)

- sitting and reading
- watching TV
- sitting inactive in public place
- passenger in a car for an hour
- Lying down to rest in afternoon
- sitting and talking to someone
- sitting quietly after lunch
- in a car stopped in traffic for a few minutes
Sleep disorders

• Insomnias  
  • Insomnia, psychiatric/medical disorders, RLS, medications
• Hypersomnias  
  • Sleep apnea, medications, Periodic leg movements of sleep
• Parasomnias (4%)  
  • Sleepwalking, sleep terrors, REM sleep behavior disorder
• Circadian rhythm disorders  
  • Shift work sleep disorder, Delayed sleep phase disorder
Differential diagnosis of abnormal sleep-related behaviors

- Parasomnias
  - REM
  - NREM
- Seizures
- Psychiatric
  - PTSD
  - Nocturnal Panic
  - Dissociative Disorders
- Frontal lobe
Parasomnias are mixtures of the primary states

- REM Behavior Disorder (RBD)
- Hypnagogic Hallucinations
- Sleep Paralysis
- ? Nightmares

- Confusional Arousals
- Sleepwalking
- Sleep Terrors
- Sleep-related eating
Causes of RBD

• Alpha synucleinopathies
  • Parkinson’s, Lewy Body, Multiple System Atrophy
• Serotonergic antidepressants
• Narcolepsy
The bad news about RBD
Antidepressants and REM Sleep Behavior Disorder: Isolated Side Effect or Neurodegenerative Signal?

Ronald B. Postuma, MD, MSc\(^1\); Jean-Francois Gagnon, PhD\(^2\); Maria Tuineiag, BSc\(^1\); Josie-Anne Bertrand, PhD\(^3\); Veronique Latreille, PhD\(^4\); Catherine Desjardins, PhD\(^2\); Jacques Y. Montplaisir, MD, PhD\(^2\)

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**Figure 2**—Kaplan-Meier life table analysis of disease-free survival in patients with idiopathic RBD according to history of antidepressant use. Cox proportional hazards \( P = 0.016 \) for antidepressant vs. no antidepressant.
Treatment of parasomnias

• Night terrors/sleepwalking
  • Short-acting benzodiazepines (eg triazolam)

• REM behavior disorder
  • Discontinue serotonergic antidepressant (if present)
  • Benzodiazepines (short, long)
  • Melatonin (6-10 mg)
  • +/- pramipexole

• Sleep-related eating disorder
  • Treat RLS, if present
  • SSRRI or topiramate