Sleep Science: Sleep, Sleepiness, and Sleeplessness

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DO YOU KNOW WHAT WEEK THIS IS?
It is DDP week!!
National Sleep Foundation announces --

DROWSY DRIVING IS PREVENTABLE.
Raise awareness by sharing our posts during Drowsy Driving Prevention Week and use #ALERT2DRIVE
sleeplessness

I don’t want to be awake: insomnia
Topics

- artist conceptions
- insomnia diagnosis
- epidemiology
- Vgontzas et al., 2001
- assessment
- CBTi
- exogenous chemicals
- hypnotics
STILL AWAKE
AT 2:00 A.M.?
insomnia diagnosis
insomnia: diagnostic criteria for chronic insomnia disorder

- complaint of difficulty initiating or maintaining sleep, early awakening
- report of daytime impairment in at least one of the following:
  - fatigue
  - cognitive functioning
  - social/occupational/school
  - mood
  - sleepiness
  - motivation/energy
  - prone to errors
  - worry about sleep
- adequate opportunity for sleep
- disturbed sleep present at least 3× week for 3 months
- not attributed to another sleep disorder

what's missing?
insomnia: causes

- brain hyperarousal
- physiological hyperarousal
- worry about sleep *
- negative conditioning
- stress: financial, social, occupational, school
- bereavement
- medical illness
- psychiatric illness
- stimulating drugs
- personality style: anxious or obsessive
Insomnia Types

- Onset
- Maintenance
- Terminal
- Mixed
epidemiology
epidemiology of insomnia

There are about 80 studies on insomnia prevalence.

- 30% of the population frequently complain of insomnia
- 8% meet diagnostic criteria
- more common in women
- occurs in all ages: most common in older adults
- older adults are disproportionately high users of hypnotics
  - high use
  - longer term use
Impact of Insomnia

• Degrades quality of life
  – impaired daytime functioning
  – sleep obsession

• Risk of hypnotic-dependent sleep disorder
  – impaired nighttime functioning
  – impaired daytime functioning

• Health risk factor
  – depression/suicide, anxiety, hypertension, drug abuse or relapse, all cause mortality
Vgontzas et al., 2001

hyperarousal
difference during 9 pm – 12:30 am
causal path?

- elevated cortisol causes insomnia
- insomnia causes elevated cortisol
- a third factor causes both
  - worry disposition
  - obsessive disposition
assessment
Assessment procedures

- sleep interview
- sleep diaries
- other sleep disorders
- PSG/actigraphy

Werner Heisenberg's warning

Heisenberg Uncertainty Principle
insomnia interview

- perceived cause of insomnia
- sleep parameters
- daytime functioning
  - anxiety, depression, fatigue, memory/attention
  - sleepiness
  - worry
- sleep history & prior treatments
- mental health, physical health, drugs
- sleep hygiene
insomnia is not a sleep deprivation disorder
## Insomnia Identity

<table>
<thead>
<tr>
<th>Poor Sleep</th>
<th>Insomnia Complaint</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>complaining poor sleeper [insomnia]</td>
<td>Absent noncomplaining poor sleeper</td>
</tr>
<tr>
<td>Absent</td>
<td>complaining good sleeper</td>
<td>Absent noncomplaining good sleeper [normal sleep]</td>
</tr>
</tbody>
</table>
Consider Other Sleep Disorders

- Sleep Apnea
- Delayed Sleep-Wake Phase Disorder
- Restless Legs Syndrome
- Periodic Limb Movement Disorder
- Narcolepsy
cognitive behavior therapy for insomnia (CBTi)

the behavioral sleep medicine 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."

Qaseem, Kansagara, Forciea, et al., 2016

American College of Physicians, 150,000 members
Spielman Model of Chronic Insomnia

**PREDISPOSING**
- hyperarousal, anxious type, decreased homeostatic drive

**PRECIPITATING**
- stress - family, health, work

**PERPETUATING**
- excessive time in bed, increase caffeine or alcohol, worry about sleep

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**Insomnia Intensity**

- **Baseline**
- **Acute Insomnia**
- **Short-term Insomnia**
- **Chronic Insomnia**

**Threshold**

Spielman et al., 1987
primary psychological treatments:

- CBTi
- relaxation
- stimulus control
- sleep restriction
- cognitive therapy
- sleep hygiene
Relaxation

- quiescent self-inquiry
- Relaxation Response (Benson, 1975)
  - quiet environment
  - object to dwell upon (monotonous stimulation)
  - passive attitude
  - comfortable position
- methods
  - dozens of methods of relaxation (e.g., progressive muscle relaxation, autogenic training, biofeedback, meditation)
  - most effective method is the one patient is willing to practice

Lichstein, 2000
stimulus control

- eliminate nonsleep activities from bedroom—reading, TV, awake in bed
- go to bed only when sleepy
- exit bedroom if awake after 15-20 min
- exit bedroom after middle of night awakening after 15-20 min
- awaken at a fixed time every day
- minimize napping

Bootzin & Epstein, 2000
sleep restriction

- determine mean TST from 2 weeks of diaries
- match TIB to TST; minimum TIB = 4.5 hours
- phone answering machine daily on TIB & TST
- if mean SE ≥ 90% for previous 5 days, increase TIB 15 min for at least next 5 days
- if mean SE < 85% for previous 5 days, decrease TIB to match mean TST of previous 5 days for at least next 10 days
- if mean SE ≥ 85% and < 90% for previous 5 days, no change in TIB
- no napping

Wohlgemuth & Edinger, 2000
cognitive therapy

- exaggerated worrisome response may contribute to initiation of insomnia
- exaggerated worry about impact of insomnia may sustain poor sleep
- dysfunctional beliefs about sleep may promote maladaptive habits
  - napping
  - excessive TIB
- treatment: recognize self-defeating beliefs and replace with constructive beliefs
- example:
  - “If I don’t get a good night’s sleep, I will be a wreck tomorrow.”
  - “If I don’t get a good night’s sleep, I may not be at my best tomorrow but I will be able to get my work done.”

Morin et al., 2000
sleep hygiene

- minimize caffeine
- minimize naps
- minimize exercise within 2 hr of bedtime (w2b)
- avoid smoking w2b
- avoid alcohol w2b
- avoid heavy meals w2b

if you are happy with your sleep, keep doing what you are doing

Riedel, 2000
summary efficacy

- 80% show meaningful improvement
- total wake time $\downarrow$ 50%
- total sleep time $\uparrow$ 30 min
- older adults respond as well as younger adults

Morin et al., 1994
secondary insomnia/comorbid insomnia

late-life insomnia

hypnotic-dependent insomnia
insomnia and other sleep disorders (apnea, restless legs) increase with age

after controlling for comorbidity and other sleep disorders, healthy elder sleep is good

Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Vitiello, Moe, & Prinz, 2002
exogenous chemicals
alcohol

- sedative
  - metabolized within a few hours
  - rebound wakefulness with alcohol withdrawal, N3 ↓
  - REM suppression ⇒ REM rebound (nightmares)

- respiratory suppressant

- commonly used by people with insomnia
caffeine

- sensitivity varies greatly between people and across lifespan
- adenosine suppression
- average cup of coffee = 100 mg
- half-life varies between 4-8 hr
- ¼ of caffeine from morning coffee active at bedtime

effects
  - SOL ↑, WASO ↑, TST ↓, N3 ↓
nicotine

- natural to tobacco
- addictive stimulant
- similar to caffeine
- effects weaker than caffeine
  - SOL ↑, WASO ↑, TST ↓, N3 ↓
hypnotics
summary truths

- No sleep medication can restore normal sleep.
- Every drug has wanted and unwanted effects.
drug processes

- pharmacodynamics
  - organ effects
  - receptor site sensitivity
  - age, gender, race, health status

- pharmacokinetics
  - drug path
  - $C_{\text{max}}$ [peak concentration]
  - $T_{\text{max}}$ [time to peak concentration]
  - $T_{1/2}$ [time to ½ concentration]
pharmacokinetics

Blood Level

Time

$T_{\text{MAX}}$ zolpidem 1.5 hr

$C_{\text{MAX}}$

$T_{1/2}$ zolpidem 2.5 hr
12 FDA approved hypnotics

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
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<tbody>
<tr>
<td>estazolam</td>
<td>Prosom</td>
</tr>
<tr>
<td>flurazepam</td>
<td>Dalmane</td>
</tr>
<tr>
<td>quazepam</td>
<td>Doral</td>
</tr>
<tr>
<td>temazepam</td>
<td>Restoril</td>
</tr>
<tr>
<td>triazolam</td>
<td>Halcion</td>
</tr>
<tr>
<td>eszopiclone</td>
<td>Lunesta</td>
</tr>
<tr>
<td>zaleplon</td>
<td>Sonata</td>
</tr>
<tr>
<td>zolpidem (Zolpimist, Intermezzo)</td>
<td>Ambien</td>
</tr>
<tr>
<td>zolpidem controlled release</td>
<td>Ambien CR</td>
</tr>
<tr>
<td>ramelteon</td>
<td>Rozerem</td>
</tr>
<tr>
<td>doxepin hydrochloride</td>
<td>Silenor</td>
</tr>
<tr>
<td>suvorexant</td>
<td>Belsomra</td>
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</tbody>
</table>
Drugs Most Commonly Used for Insomnia in 2002

Occurrences (Millions)

- Trazodone: 2.7
- Zolpidem: 2.1
- Amitriptyline: 0.8
- Temazepam: 0.7
- Quetiapine: 0.6
- Zaleplon: 0.5
- Clonazepam: 0.4
- Hydroxyzine: 0.4
- Alprazolam: 0.3
- Lorazepam: 0.3
- Olanzapine: 0.3
- Flurazepam: 0.2
- Doxepin: 0.2
- Cyclobenzaprine: 0.2
- Diphenhydramine: 0.2

* not FDA approved for insomnia

Walsh, 2004
Hypnotic Advantages

- Convenience
- Short-term efficacy
- Most appropriate for:
  - adjustment insomnia, jet lag
  - intrusive comorbid insomnia
  - chronic insomnia with intermittent dosing
Hypnotic Disadvantages

- REM & N3 suppression
- Daytime impairment
  - cognitive functioning
  - alertness
  - balance
  - anterograde amnesia
- Impairment during the sleep period
- Rebound insomnia/anxiety/nightmares with abrupt withdrawal
Hypnotic Risks

- Tolerance-dependence
  - “hypnotic-dependent sleep disorder”
- Automobile accidents
- Accidental falls
FDA.gov safety concerns

- **daytime impairment**
  - “FDA warns of next-day impairment with sleep aid Lunesta (eszopiclone) and lowers recommended dose.”
  - “FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR.”

- **women**
  - “FDA has informed the manufacturers that the recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR).”

- **elderly and infirm**
  - “Elderly or debilitated patients may be especially sensitive to the effects of Ambien (zolpidem tartrate). Patients with hepatic insufficiency do not clear the drug as rapidly as normals. An initial 5 mg dose is recommended in these patients.”
## Sampling Major Side Effects, FDA Webpage

<table>
<thead>
<tr>
<th>zolpidem (Ambien)</th>
<th>eszopiclone (Lunesta)</th>
<th>suvorexant (Belsomra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal thinking and behavioral changes (hallucinations, sleep driving, suicidal thoughts)</td>
<td>Unpleasant taste in mouth, dry mouth, drowsiness, dizziness, headache, symptoms of the common cold</td>
<td>Sleepiness during the day, not thinking clearly, act strangely, confused, or upset, “sleep-walking” or doing other activities when you are asleep like eating, talking, having sex, or driving a car</td>
</tr>
</tbody>
</table>
patient reviews of Belsomra

the first 2 reviews that came up:

1. “Belsomra is the miracle I have been waiting for my whole life.”

2. “Worst garbage I've ever taken to help me sleep.”
risk of car wrecks, all ages

hypnotic benzodiazepines

user nonuser

relative risk

0 1 2 3 4 5

Neutel, 1995
older adults risk of hip fracture

Wang, Bohn, Glynn, et al., 2001
Frey, Ortega, Wiseman, et al., 2011

percent failed balance beam walk
5 mg zolpidem

percent failed
0
10
20
30
40
50
60
70

subjects
younger older

practice
wake
sleep/placebo
sleep/zolpidem

Frey, Ortega, Wiseman, et al., 2011
Other

diphenhydramine (Benadryl)
melatonin
valerian
**BZ/NBZ Sleep Effects**

<table>
<thead>
<tr>
<th>Change Type</th>
<th>PSG</th>
<th>Diary</th>
</tr>
</thead>
<tbody>
<tr>
<td>△PSG SOL</td>
<td>↓11.4</td>
<td>↓18.3</td>
</tr>
<tr>
<td>△PSG WASO</td>
<td>↓11.9</td>
<td>↓27.5</td>
</tr>
<tr>
<td>△PSG TST</td>
<td>↑22.0</td>
<td>↑42.0</td>
</tr>
</tbody>
</table>

*Buscemi et al., 2007*

11 minutes
to be continued