

No, I have not slept well...



Why do you ask?

Sleep as Symptom¹

Diagnosing and Fixing the
Underlying Cause(s) of Insomnia

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NANP Annual Conference and Expo

April 3, 2020
Newport Beach, CA

Disclosures

- ▶ Nutritional Biochemistry, Inc. (NBI), Founder and President
- ▶ NBI Pharmaceuticals, Founder and President
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NBI Sleep Relief

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SLEEP RELIEF
60
**BI-PHASIC,
TIME-RELEASE
TABLETS**

Average Sleep Duration of Adults (U.S.)

- ▶ Average nightly sleep time is 6.9 h
- ▶ 20% of adults sleep less than 6.5 h per night
- ▶ Sleep decreased 20% over the last century
- ▶ 1998-2005:
 - ▶ Sleeping ≥ 8 h on weekdays decreased by 9%
 - ▶ Sleeping < 6 h of sleep on weekdays increased by 4%
- ▶ An average optimal sleep time is now considered 8.2 h per night

Epidemiology of Sleep Disturbances

- ▶ 50 to 70 mn Americans chronically suffer from a disorder of sleep and wakefulness
- ▶ Insomnia: effects 10-15% of the general population
 - ▶ Prevalence of insomnia in primary care patients estimated as high as 69%.
 - ▶ Transient insomnia (< 2 weeks duration) affects up to 80%
- ▶ Sleep apnea: effects about 10% of the population
- ▶ RLS and periodic limb movement disorder: approx 5-9%.

Epidemiology Citations

- ▶ Kurshid K. A Review of Changes in DSM-5 Sleep-Wake Disorders. *Psychiatric Times*. 2015. <http://www.psychiatrictimes.com/special-reports/review-changes-dsm-5-sleep-wake-disorders>. Accessed January 5, 2018.
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- ▶ Pagel JF, Parnes BL. Medications for the Treatment of Sleep Disorders: An Overview. *Prim Care Companion J Clin Psychiatry*.2001;3(3):118-125.
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Health System Impacts

- ▶ Increases risk of hypertension, diabetes, obesity, depression, heart attack, stroke, death.
- ▶ \$16 billion each year in medical care
- ▶ Approx. 20% of all serious car crash injuries associated with driver sleepiness, independent of alcohol effects.

Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. In: Colton H, Altevogt B, eds: The National Academies Press; 2006:424

Kurshid K. A Review of Changes in DSM-5 Sleep-Wake Disorders. *Psychiatric Times*. 2015. <http://www.psychiatrytimes.com/special-reports/review-changes-dsm-5-sleep-wake-disorders>. Accessed January 5, 2018.

Insomnia Effects

- ▶ greater daytime fatigue
- ▶ decreased mood and depression
- ▶ more anxiety or stress
- ▶ less vigor
- ▶ difficulty coping with life demands
- ▶ difficulty completing tasks
- ▶ Impaired job performance, social life and family life.
- ▶ decreased quality of life (QOL) similar to congestive heart failure (CHF) and major depressive disorder

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Sleep Benefits: Inverted U-Shaped Curve?

- ▶ Habitually short sleep durations (typically <6 hours) and long sleep durations (≥ 9 hours)
- ▶ Hypertension: only in short sleepers (HR 2.10, $p < 0.05$).
- ▶ Diabetes:
 - ▶ Short sleepers (5 or less hrs), RR 1.29 (1.05-1.58)
 - ▶ Long sleepers (9 or more hrs), RR 1.32 (1.07-1.62)
- ▶ Metabolic syndrome: short & long sleepers, 45% increase compared to 7-8 hrs.
- ▶ Mortality: male short sleepers, 4x greater risk (OR = 4.00, CI 1.14-13.99, $p < 0.05$).

Citations

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- ▶ Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory J, Manuck SB. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. *Sleep* 2008;31:635–643.
- ▶ Vgontzas AN, Liao D, Pejovic S, et al. Insomnia with short sleep duration and mortality: the Penn State cohort. *Sleep*.2010;33(9):1159-1164.
- ▶ Watanabe M, Kikuchi H, Tanaka K, Takahashi M. Association of short sleep duration with weight gain and obesity at 1-year follow-up: a large-scale prospective study. *Sleep* 2010;33:161–167

Insomnia Diagnosis (DSM-5)

- ▶ The predominant complaint of **dissatisfaction with sleep quantity or quality** is associated with one or more of: (1) difficulty initiating sleep, (2) difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings, (3) early-morning awakening with inability to return to sleep.
- ▶ The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
- ▶ Occurs **at least three nights per week**.
- ▶ Present **for at least three months**.

Insomnia Diagnosis (cont'd)

- ▶ Occurs despite adequate opportunity for sleep.
- ▶ Not better explained by and does not occur exclusively during course of another sleep-wake disorder.
- ▶ Not attributable to the physiological effects of illicit substances or medications.
- ▶ Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Sleep Stages

NREM

- ▶ Stage 1:
 - ▶ Easily interrupted by noise
 - ▶ From middle-aged onwards, more time is spent in stage I sleep with more awakenings.
- ▶ Stage 2: Requires more intense sleep stimuli to wake up
- ▶ Stage 3: The “restful” component of sleep that makes you feel refreshed after sleeping
- ▶ Stage 4: Highest arousal threshold for all NREM stages

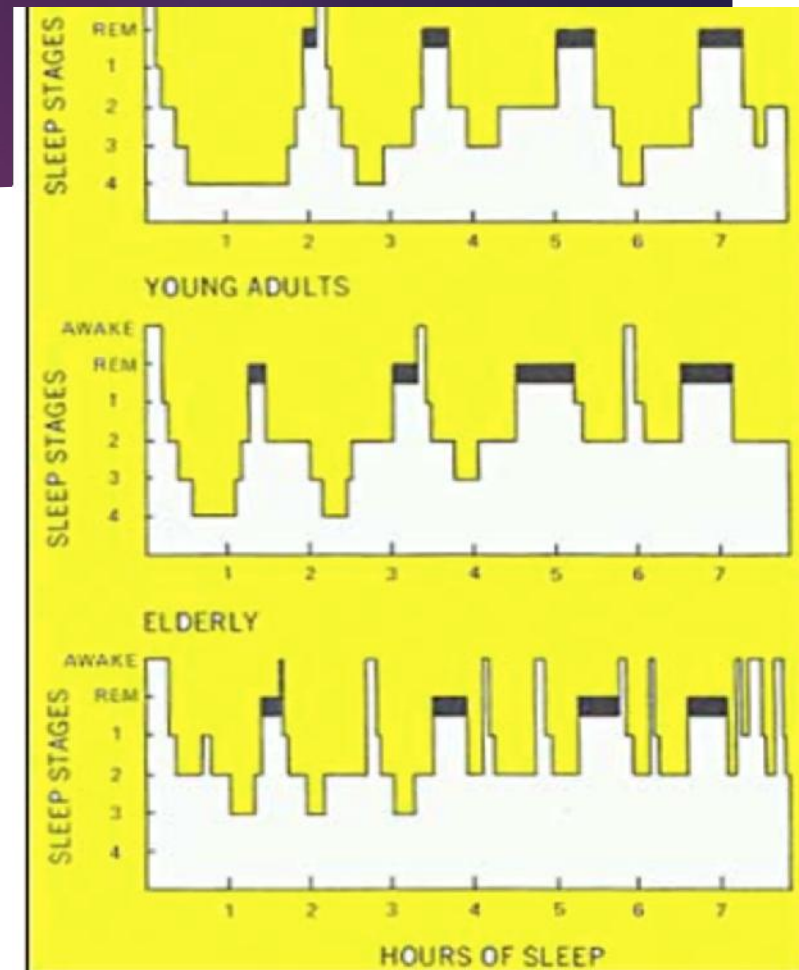
REM

- ▶ Muscle atonia (cataplexy)
- ▶ REM sleep tends to be preserved until quite late in life
- ▶ Penile erections

Effects of Age on Sleep Cycles

14

- ▶ Normal sleep latency: < 30 min (young), < 45 min (elderly)
- ▶ REM sleep (darkened area) occurs cyclically at approx. 90-minute intervals (all age groups)
- ▶ REM sleep: decreases slightly in the elderly
- ▶ Deep sleep or slow wave sleep (SWS) (stages 3 and 4) gradually lessens with age and usually disappears in the elderly.
- ▶ Elderly patients: frequent awakenings and a notable increase in wake time after sleep onset

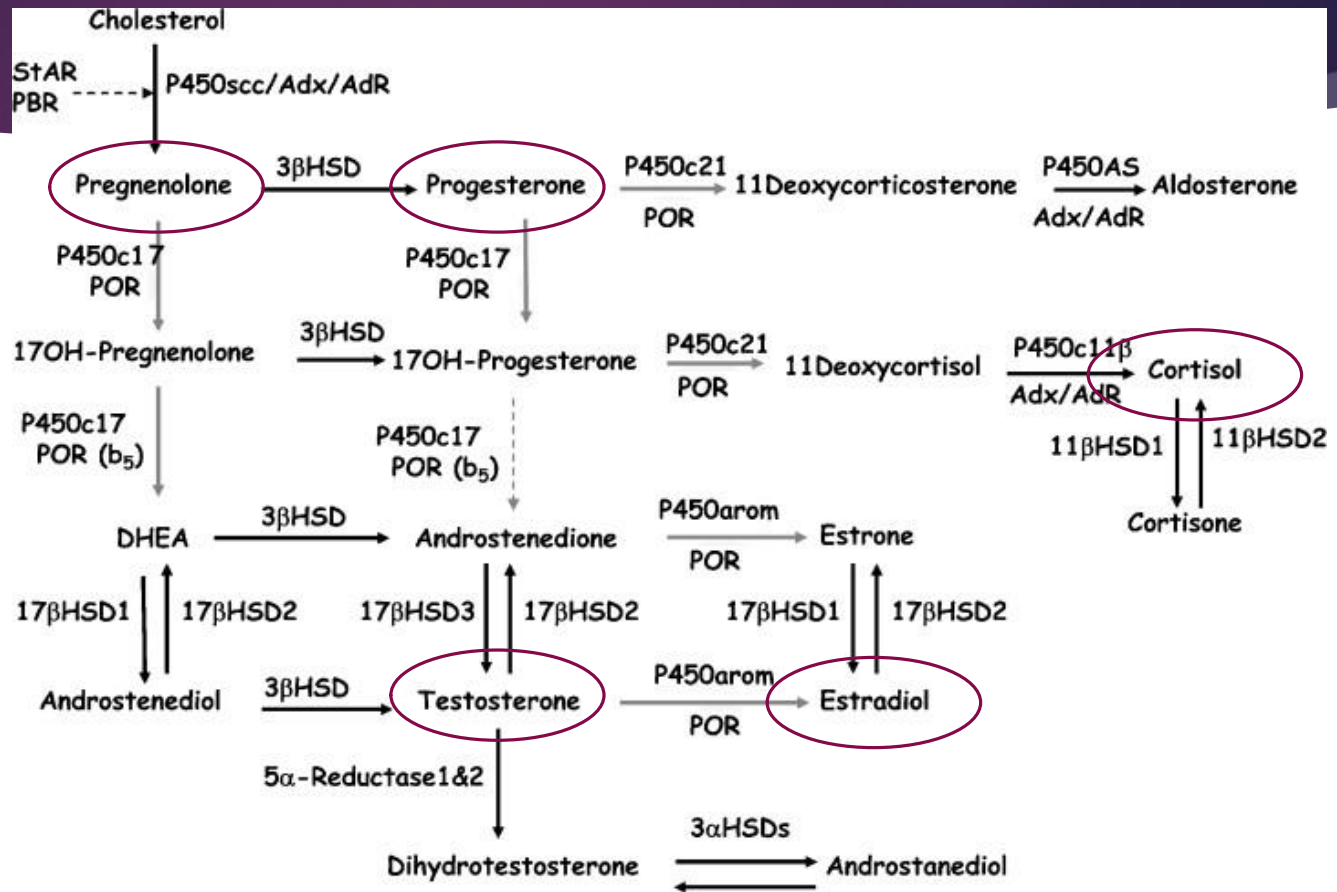


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Wichniak A, Wierzbicka A, Walecka M, Jernajczyk W. Effects of Antidepressants on Sleep. *Curr Psychiatry Rep.* 2017;19(9):63.

Insomnia in TBI

- ▶ Can appear as trouble initiating or maintaining sleep.
- ▶ One study of 452 patients: 50% reported insomnia symptoms.
- ▶ Can be delayed sleep–wake phase disorder or irregular sleep–wake rhythm disorder.
- ▶ Military personnel: multiple brain injuries were found to lead to an increased risk for insomnia.
- ▶ See work by Mark Gordon, MD
 - ▶ <http://www.millenniumhealthcenters.com/index.html>

Steroid Hormones

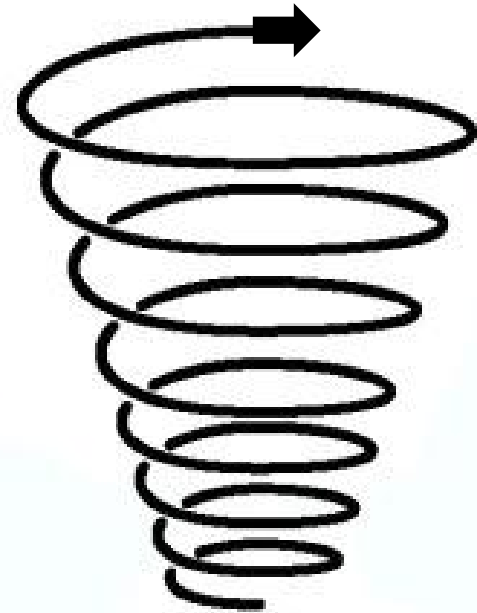


Sleep and Gender

- ▶ Top risk factors for insomnia: gender and age
- ▶ Women are at a 40% greater risk for insomnia throughout their lifetime compared with men
- ▶ Studies from multiple countries indicate that the increased prevalence of insomnia in women compared to age-matched men is a global phenomenon, suggesting that a woman's physiology is a significant consideration in insomnia.
- ▶ Insomnia in women and girls: strongly assoc. with a 2x greater risk of depression.
- ▶ Relationship among ovarian steroids and sleep is poorly understood.

The HPA Spiral

“If elevated HPA activity before sleep promotes sleep fragmentation, sleep fragmentation and sleep loss have in turn been shown to increase evening cortisol levels...Taken together, these data suggest the occurrence of a vicious circle that could be responsible for the chronicity of insomnia.”



Insomnia HPA Access

- ▶ Shorter & poor quality sleep associated with changes in diurnal cortisol
- ▶ SWS inhibits HPA axis
- ▶ Activation of HPA axis or administration of glucocorticoids → arousal and sleeplessness
- ▶ Insomnia associated with a 24 hour ↑ ACTH and cortisol, consistent hyperarousal

Cortisol and Sleep

- ▶ Administration of glucocorticoids → arousal and sleeplessness.
- ▶ In normal individuals, wakefulness and stage 1 sleep (light sleep) accompany cortisol increases.
- ▶ SWS associated with ↓ plasma cortisol levels.
- ▶ Induced sleep disruption (frequently repeated arousals) associated with significant ↑ plasma cortisol levels.
- ▶ Mean 24 hour plasma cortisol significantly higher in people with shorter total sleep time than those with a longer total sleep time

Cortisol, Aging and Sleep

- ▶ **Middle aged men show increased vulnerability of sleep to stress hormones**
 - ▶ → ↓ quality of sleep during periods of stress.
- ▶ **Increasing age associated with increasing evening cortisol levels**
 - ▶ +19.3 nmol/L per decade; $P < .001$
 - ▶ Significant only after age 50 when sleep became more fragmented and REM sleep declined
- ▶ Effect of aging on levels and diurnal variation of adrenocorticotrophic activity may be involved in the etiology of poor sleep in the elderly

Hormones & Sleep Citations

- ▶ Abell JG, Shipley MJ, Ferrie JE, Kivimaki M, Kumari M. Recurrent short sleep, chronic insomnia symptoms and salivary cortisol: A 10-year follow-up in the Whitehall II study. *Psychoneuroendocrinology*. 2016;68:91-99.
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Hyperarousal Hypothesis: Tired but Wired

- ▶ Sleepiness vs Fatigue
- ▶ Sleepiness: sleep apnea, narcolepsy, and sleep deprivation.
- ▶ Fatigue: chronic insomnia, sleep disturbances in the elderly, and psychogenic hypersomnia.
- ▶ Distinction between “sleepiness” and “fatigue” adopted unanimously for insomnia research by an expert panel of 25 sleep researchers in 2005 .
- ▶ Insomnia patients commonly show increased glucose metabolism in multiple brain areas
- ▶ Insomnia associated with a 24 hour \uparrow ACTH and cortisol, consistent hyperarousal.

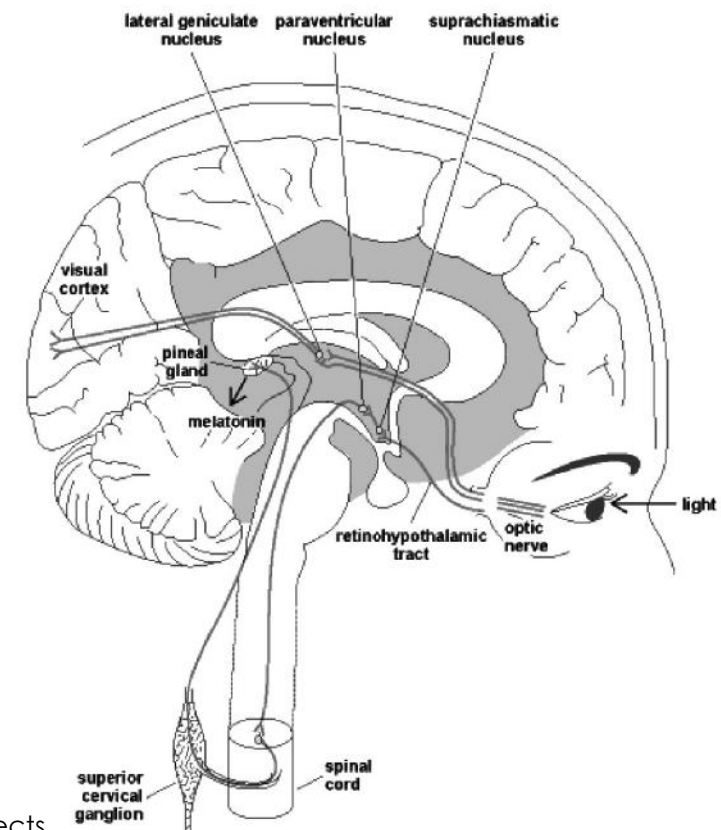
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Light-Emitting (LE) Devices, Melatonin & Sleep

- ▶ Examples: mobile phones, tablets.
- ▶ N= 12 healthy adults (mean \pm SD: 24.92 \pm 2.87 y; 6 women, 6 men)
- ▶ Duration: 14-d
- ▶ Design: randomized, crossover design; inpatient setting
- ▶ Conditions:
 1. reading an LE-eBook in otherwise very dim room light for ~4 h before bedtime for five consecutive evenings
 2. reading a printed book (same duration)



Chang AM, Aeschbach D, Duffy JF, Czeisler CA. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. *Proc Natl Acad Sci U S A*. 2015;112(4):1232-1237.

LE Devices, Melatonin & Sleep (cont'd)

- ▶ Measurements: Sleep latency, total sleep time (TST), sleep efficiency (% of time spent in bed), time spent in each sleep stage, plasma melatonin. Subjective sleepiness also rated.
- ▶ Results for melatonin ($p < 0.001$):
 - ▶ **E-book reading: suppressed evening melatonin by $55.12 \pm 20.12\%$**
 - ▶ Print book: no melatonin suppression.
 - ▶ **Dim light melatonin onset was >1.5 h later on the day following the LE-eBook condition ($22:31 \pm 0:42$) than in the print-book condition ($21:01 \pm 0:49$)**
- ▶ **Sleep latency: E-book \rightarrow 10 minutes longer to fall asleep vs. print book (mean \pm SD, 25.65 ± 18.78 min vs. 15.75 ± 13.09 min; $p = 0.009$).**

LE Devices, Melatonin & Sleep (cont'd)

- ▶ REM: rapid eye movement (REM) sleep following e-book (109.04 ± 26.25 min vs. 120.86 ± 25.32 min print book; $p = 0.03$)
- ▶ No differences for TST, sleep efficiency, or the duration of non-REM sleep.
- ▶ Evening sleepiness: e-book associated with decreased sleepiness an hour before bedtime ($p < 0.01$), and EEG showed less power within the delta/theta frequency range (1.0–7.5 Hz).
- ▶ Morning sleepiness:
 - ▶ **E-book participants felt sleepier the morning after reading an e-book the prior evening ($p < 0.001$).**
 - ▶ **Took them hours longer to fully “wake up” and attain the same level of alertness than in the printed book condition.**

LE Devices, Melatonin & Sleep (cont'd)

- ▶ “The results of this study are of particular concern, given recent evidence linking chronic suppression of melatonin secretion by nocturnal light exposure with the increased risk of breast, colorectal, and advanced prostate cancer associated with night-shift work which has now been classified as a probable carcinogen by the World Health Organization”

Medication Causing Sleep Disruption

Indication	Drug	Effect
Anti-arrhythmics	procainamide (Procanbid), quinidine (Cardioquin), disopyramide (Norpace)	Nighttime sleep difficulties, daytime fatigue
Beta blockers	atenolol (Tenormin), metoprolol (Lopressor), propranolol (Inderal)	Insomnia, nighttime awakenings, nightmares
Clonidine	Clonidine (Catapres)	Daytime drowsiness and fatigue, disrupted REM sleep; less commonly, restlessness, early morning awakening, nightmares
Corticosteroids		Daytime jitters, insomnia
Diuretics		Increased nighttime urination, painful calf cramps during sleep
Medications containing alcohol	Coricidin HBP, Nyquil Cough, Theraflu Warming Relief	Suppressed REM sleep, disrupted nighttime sleep
Medications containing caffeine	NoDoz, Vivarin, Caffeine	Wakefulness that may last up to six to seven hours

Medications that can affect sleep. *Harvard Women's Health Watch* 2010; https://www.health.harvard.edu/newsletter_article/medications-that-can-affect-sleep. Accessed December 28, 2017.

Medication Causing Sleep Disruption

Indication	Drug	Effect
Nicotine replacement products	nicotine patches (Nicoderm), gum (Nicorette), nasal spray or inhalers (Nicotrol), and lozenges (Commit)	Insomnia, disturbing dreams
Sedating antihistamines	diphenhydramine (Benadryl), chlorpheniramine (Chlor-Trimeton) dimenhydrinate (Dramamine)	Drowsiness
Selective serotonin reuptake inhibitors (SSRIs)	fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil)	Decreased REM sleep, daytime fatigue
Sympathomimetic stimulants	dextroamphetamine (Dexedrine), methamphetamine (Desoxyn), methylphenidate (Ritalin)	Difficulty falling asleep, decreased REM and non-REM deep sleep
Theophylline	theophylline (Slo-bid, Theo-Dur, others)	Wakefulness similar to that caused by caffeine
Thyroid hormone	levothyroxine (Levoxyl, Synthroid, others)	Sleeping difficulties (at higher doses)

Insomnia Medications

- ▶ Sedative Hypnotics (The “Z-drugs”)
 - ▶ DEA Schedule IV Drugs
 - ▶ Benzodiazepines
 - ▶ Short acting: Triazolam (Halcion)
 - ▶ Intermediate-acting: Estazolam (ProSom)
 - ▶ Long-acting: Quazepam (Doral)
 - ▶ Benzo-like: Zolpidem (Ambien), Eszopiclone (Lunesta), Zaleplon (Sonata)
- ▶ Orexin receptor antagonist: Suvorexant (Belsomra)
- ▶ Sedating Antidepressants
- ▶ Antihistamines

Z-Drug

- ▶ “Z-drugs”: benzodiazepines and non-benzodiazepines
 - ▶ GABA-A receptor modulators
 - ▶ For insomnia with increased sleep latency and shorter sleep duration
 - ▶ Does not improve sleep quality
 - ▶ Fail to improve and even adversely affect daytime vigilance
 - ▶ The number needed to treat for improved sleep quality was 13 and the number needed to harm for any adverse event was 6. An AE is more than twice as likely as improving sleep.
- ▶ Risk: falls, dizziness, lightheadedness
- ▶ **“In people over 60, the benefits associated with sedative use are marginal and are outweighed by the risks, particularly if patients are at high risk for falls or cognitive impairment”**

Hypnotics for Insomnia

- ▶ 2010: 6-10% of US adults took a hypnotic drug for sleep
- ▶ N = 10,529 patients who took a hypnotic vs 23,676 matched controls
- ▶ Duration: followed on average for 2.5 years
- ▶ **HR for death compared to controls** ($p < 0.05$):
 - ▶ 0.4-18 doses per year: HR 3.60 (2.92 to 4.44)
 - ▶ 18-132 doses per year: HR 4.43 (3.67 to 5.36)
 - ▶ >132 doses per year: HR 5.32 (4.50 to 6.30)
- ▶ **Cancer risk:** > 132 doses resulted in HR of 1.35

Hypnotics for Insomnia (cont'd)

- ▶ Rx: Zolpiden, Tamazepam, Eszopiclone
- ▶ **Hypnotics may be associated with 320,000 to 507,000 excess deaths in the US.**
- ▶ Excellent follow up review: Kripke DF. Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit. *F1000Res.* 2016;5:918.

Insomnia Causes

Medical Conditions	Psychological	Lifestyle	Environmental
Pain	Depression	Social jetlag	Bedroom temp.
Drugs/alcohol use or withdrawal	Anxiety	Screens before bed	Noise
Thyrotoxicosis	Life stressors		Eating, exercise, caffeine or alcohol before bed
Dyspnea	Bedtime worrying		Jet lag
Hormone imbalances	Conditioning		Shift work
	Mania or hypomania		Daytime napping
	Sleep as attachment behavior		

Sleep as Attachment Behavior

- ▶ Sleep can be considered as a fundamental attachment behavior, in that it's a behavioral state that requires a relative cessation of awareness and down-regulation of vigilance—processes that are optimized when one feels a sense of physical and emotional safety and security.
- ▶ Spouses' report of insomnia symptoms inversely associated with marital happiness, even after accounting for one's own sleep problems.
 - ▶ fair or poor physical health, depressed mood, fair or poor mental health, not happy, low optimism, feeling left out, not satisfied with relationships, and unhappy marriage.
- ▶ In a study of midlife women drawn from the Study of Women's Health Across the Nation, **higher levels of marital happiness were associated with lower rates of insomnia symptoms.**

Sleep Domains

- ▶ Quantitative aspects:
 - ▶ duration of sleep
 - ▶ sleep latency
 - ▶ and times woken during sleep (arousals)
- ▶ Subjective aspects:
 - ▶ depth
 - ▶ restfulness
 - ▶ refreshment

Fitbit: What 6 Billion Data Points Show

- ▶ Fitbit began tracking sleep stages in March 2017
- ▶ Collected data from more than 6 billion nights' sleep
- ▶ The largest data set ever collected.
- ▶ The biggest finding in Fitbit's data may be the link between sleep quality and bedtime consistency.
 - ▶ If your bedtime varies by two hours over the week, you'll average half hour of sleep a night less than someone whose bedtime varies by only 30 minutes.
 - ▶ "Social jet lag"

<https://finance.yahoo.com/news/exclusive-fitbits-6-billion-nights-sleep-data-reveals-us-110058417.html>
<https://blog.fitbit.com/sleep-study/>

Sleep Latency

- ▶ Anxiety
 - ▶ General
 - ▶ Specific regarding sleep itself
- ▶ TBI history
 - ▶ Endocrine dysfunction
 - ▶ Skeletal misalignment: causing pn; decreased cerebrospinal circulation
- ▶ Medications
- ▶ Sleep hygiene
- ▶ Conditioning
 - ▶ Muse (<http://www.choosemuse.com/>)
 - ▶ Mind-body: meditation

Sleep Fragmentation

- ▶ Regular pattern?
 - ▶ Dietary assessment: blood sugar dysregulation
- ▶ Irregular pattern?
 - ▶ Assess for cognitive decline (could be early AD indicator)
 - ▶ Nocturia? Men: BPH? Men and women: drinking liquids too late?
 - ▶ GERD?
 - ▶ Anxiety?
 - ▶ RLS? Magnesium, glycine, iron?
- ▶ Sleep hygiene?
- ▶ Anxiety?
- ▶ Ease of falling back asleep after waking up?

Treatment Options

- ▶ Sleep hygiene
- ▶ Diet: blood sugar-regulating diet
- ▶ Lifestyle: stress reduction
- ▶ Exercise: Yoga
- ▶ Mind-Body-Spirit: counseling, CBT, mindfulness-based meditation
- ▶ Dietary supplements
- ▶ Hormone replacement
- ▶ Medications

Sleep Hygiene

- ▶ Room temperature
- ▶ No screens
- ▶ Dark room
- ▶ Appropriate ambient noise
- ▶ Meditation

Diet

- ▶ No caffeine at night
- ▶ Stop drinking liquids a couple of hours before bed (adjust as necessary)
- ▶ Blood-sugar regulation:
 - ▶ whole foods diet (Mediterranean Diet)
 - ▶ If suffering from sleep disruption, try eating a protein snack at bedtime.
- ▶ Mediterranean Diet

Mediterranean Diet

- ▶ Older adults (avg age approx. 69 yrs):
 - ▶ An unchanged MD score from Exam 1 to Exam 2 was associated with adequate sleep duration, less insomnia symptoms, and less likely to have insomnia accompanied by short sleep (all $p < 0.05$)
 - ▶ An increase in the MD score was not associated with insomnia symptoms.
- ▶ Adolescents (avg age 12.5 yrs):
 - ▶ Sleep duration: adherence to the MD associated with sleep duration ($p = 0.025$), with sleep duration found to be adequate in the medium and high adherence to the MD groups.
 - ▶ Daytime sleepiness: significant differences among adherence to the MD categories and daytime sleepiness were reported ($p < 0.005$) with higher drowsiness (higher PDSS scores) found in the students who had a lower MD score.

Castro-Diehl C, Wood AC, Redline S, et al. Mediterranean diet pattern and sleep duration and insomnia symptoms in the Multi-Ethnic Study of Atherosclerosis. *Sleep*. 2018;41(11).

Rosi A, Giopp F, Milioli G, et al. Weight Status, Adherence to the Mediterranean Diet, Physical Activity Level, and Sleep Behavior of Italian Junior High School Adolescents. *Nutrients*. 2020;12(2).

Mindfulness Based Stress Reduction (MBSR)

- ▶ RCT, pilot study (N = 30, 22 women, 8 men)
 - ▶ 20 in MBSR and 10 in pharmacotherapy (PCT) arm
- ▶ Inclusion criteria: ages 18-65 years with primary insomnia.
- ▶ MBSR Format:
 - ▶ 8 weekly, 2.5 hours classes, and a day-long retreat.
 - ▶ Meditation techniques included: body-scan, standing, sitting and walking meditations, and gentle Hatha yoga.
 - ▶ A 6-hour silent retreat was held on the weekend between weeks 6 and 7.
 - ▶ Home practice expectations were 45 minutes of meditation per day at least 6 days a week for 8 weeks, followed by 20 minutes per day for 3 months.

MBSR for Primary Insomnia

- ▶ Sleep latency: decreased 8.9 minutes ($p = 0.04$)
- ▶ Insomnia related activity impairment: significantly improved ($p < 0.01$)
- ▶ "By 5-months, over half the MBSR patients had recovered"
 - ▶ **50% of MBSR participants no longer met the diagnostic criteria for insomnia**
- ▶ All but one of the MBSR patients whose total sleep time averaged less than 6 hours at baseline was reliably sleeping more than 6 hours per night.
- ▶ Compliance with MBSR: 90%
- ▶ Reductions in Dysfunctional Beliefs about Sleep and Activity Limitation due to Insomnia from baseline to month 5 were significantly predicted by home practice during the active intervention period ($p < .02$).

Cognitive Behavioral Therapy

- ▶ Studies have demonstrated that, for primary insomnia, CBT-I is equal to pharmacological treatment in the short-term and has longer lasting effects.

Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Med Rev.* 2009;13(3):205-214.

Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract.* 2012;13:40.

Nutritional Approaches

Nutrient

Relaxing

- Skullcap (*Scutellaria baicalensis*)
- Kava (*Piper methysticum*)
- St. John's Wort (*Hypericum perforatum*)
- German chamomile (*Matricaria recutita*)
- Hops (*Humulus lupulus*)
- Gotu kola (*Centella asiatica*)
- Valerian root (*Valeriana officinalis*)
- Passionflower (*Passiflora incarnate*)
- Lemon balm (*Melissa officinalis*)
- GABA
- Glycine
- Magnesium
- L-theanine

Serotonergic & Melatonergic

- Tryptophan
- 5-HTP
- Rhodiola (*Rhodiola rosea*)
- *Angelica sinensis*
- Hyperforin from St. John's Wort (*Hypericum perforatum*)
- Melatonin

Citations

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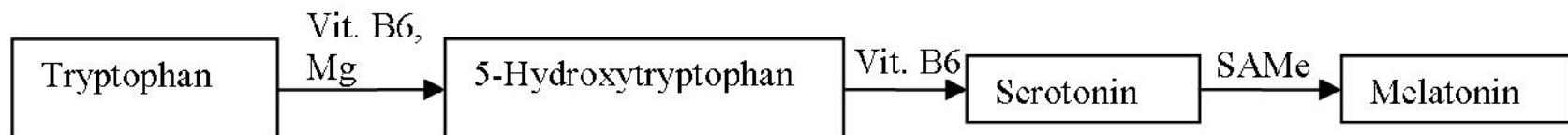
Melatonin

- ▶ Secreted from pineal gland and several extrapineal sites
- ▶ Melatonin is formed in numerous organs and cells, such as the gastrointestinal tract (GIT), bone marrow, several leukocytes, membranous cochlea and, presumably, skin and other regions of the central nervous system.
- ▶ **Owing to the size of the organ, the amounts of melatonin present in the GIT are several hundred-fold higher than those in the pineal gland.**

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Melatonin



Tryptophan-to-Melatonin Pathway

Melatonin (cont'd)

- ▶ Physiological concentrations:
 - ▶ Young/middle aged subjects: 100–150 pg/ml
 - ▶ Elderly: 34.5 +/- 15.4 pg/ml
- ▶ 24 hour endogenous melatonin secretion follows a typical circadian pattern:
 - ▶ rise in melatonin around 10:00 pm
 - ▶ peak concentration around 2:00 am
 - ▶ declines at approximately 6:00 am
- ▶ Nocturnal production of the hormone is impaired in older adults

Melatonin (cont'd)

- ▶ Melatonin production declines with age and is lower in middle aged and elderly patients with insomnia than in good sleepers.
- ▶ Strong reductions of circulating melatonin are also observed in numerous disorders and diseases, including:
 - ▶ Alzheimer's disease and other neurological and stressful conditions
 - ▶ Pain
 - ▶ Cardiovascular diseases
 - ▶ Cancer
 - ▶ Endocrine and metabolic disorders, in particular diabetes type 2.

Melatonin

- ▶ Table: Diseases associated with decreased melatonin

Disease/disorder	Comments
Alzheimer's disease	Stage dependent decreases down to complete loss of melatonin rhythm
Pick's disease	Two cases only
Autism spectrum disorders	Decreases in melatonin or urinary 6-sulfatoxy-melatonin frequent, but not generally observed
Schizophrenia	Only in a subpopulation
Multiple sclerosis with major depression	Not observed in major depression alone
Primary obsessive compulsive disorder	
Menière's disease	Possibly related to stress by tinnitus and vertigo
Macular degeneration	
Cases of severe epilepsy	High interindividual variation. However, increases during seizures
Coronary heart disease, myocardial infarction, cardiac syndrome X	
Fibromyalgia	Decreases observed in women Uncertainties concerning levels Pain reduced by melatonin
Neuralgia	
Migraine	Pain reduced by melatonin
Bulimia	
Critical illness	
Postoperative stress	Decreases in patients without complications, but strong increases in those with delirium
Hypothalamic hamartoma	
Craniopharyngioma	
Endometrial cancer	
Non-small cell lung cancer	In part caused by pain?
Acute intermittent porphyria	Further decreased by seizures
Hypergonadotrophic hypogonadism	
Diabetes type 2	

Melatonin Replacement

- ▶ Exogenous melatonin uses:
 - ▶ Chronobiotic (to shift circadian phase)
 - ▶ Antioxidant
 - ▶ Oncostatic agent
 - ▶ Decrease micturation in men with BPH
 - ▶ Improve bone mineral density
- ▶ Men with BPH treated with 2 mg of melatonin generally experience a 10% reduction in episodes of nocturia. ($p < 0.05$)
- ▶ Exogenous melatonin can restore a normal circadian rhythm of micturition and improve sleep.

Melatonin Citations

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Case 1: 43-yr-old female

- ▶ Sleep: 6-7 hours qd; (+) Sleep phase advance: Wakes 3 am, without apparent cause. Frequently difficult to fall back to sleep.
- ▶ Marital status: Happily married, three children (7 to 13 years old)
- ▶ Stress: "moderate" (about 6-10, with 10 worst)
- ▶ Diet: 24 hr diet recall
- ▶ (+) Postprandial somnolence approx. 2 hours after lunch
- ▶ Exercise: occasional, not regular.
- ▶ Treatment:
 - ▶ Emphasize protein at each snack and meal.
 - ▶ 8-10 grams of protein at bedtime.
 - ▶ Help her transition to more of a Mediterranean Diet
- ▶ Results: Sleep problem resolved.

Case 2: Insomnia in 50-yr-old male

- ▶ Duration: “it’s been a problem for years.”
- ▶ Marital status: happily married, 2 children (4 and 7 years old)
- ▶ Mood: “low”
- ▶ + erectile dysfunction
- ▶ + History multiple TBI’s
- ▶ Sleep: avg 5 hrs qd; (+) SPD and (+) SPA about 4x qwk ppr
- ▶ 24-hr diet recall.
- ▶ Testing:
 - ▶ TSH: well controlled with levothyroxine
 - ▶ Total Testosterone: 213 (241-827)
 - ▶ Free Testosterone: 61 (47-244)
- ▶ Stress: “high,” 8/10 with 10 worst
- ▶ Exercise: Regular, moderate, 3-4x qwk

Case 2 (cont'd)

- ▶ Treatment:
 - ▶ Transition to more of a Mediterranean Diet pattern
 - ▶ testosterone replacement therapy
 - ▶ Stress reduction
 - ▶ NBI Sleep Relief dietary supplement
- ▶ Results:
 - ▶ sleep improved: average 7-8 hours sleep per night. When he wakes up in the middle of the night, it's easier to fall back asleep.
 - ▶ Other symptoms of Low T improved:

Sweet Dreams



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