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Cardiometabolic Health Congress

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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Sleep Disorders: Classification, Screening, Treatment, and Impact on Cardiometabolic Risk

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Founder, American Academy of Cardiovascular Sleep Medicine
President, Empire Sleep Medicine

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Outline

- ***Part 1:***
- Normal Sleep Physiology
- Effect of Sleep on Common Medical Disorders
- Impact of Insufficient Sleep
- Understanding and Treating Insomnia
- Obstructive Sleep Apnea
- Restless Legs Syndrome
- Narcolepsy
- ***Part 2:***
- Cardiology and Sleep Apnea – The Intersection and Collision: A Deeper Dive

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Normal Sleep Physiology

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Normal Sleep

- Sleep cycling and regulation
  - Sustained immobility and quiescence
  - Reduced responsiveness to external stimuli
  - Sequence of stages with characteristic brain wave patterns
- Normal physiologic changes during sleep
  - Temperature, Ventilatory, hemodynamic, etc.
- Effects of sleep on common medical disorders
  - Cardiovascular, Immune system, CNS, Hemodynamic, etc.
- Impact of chronic sleep debt

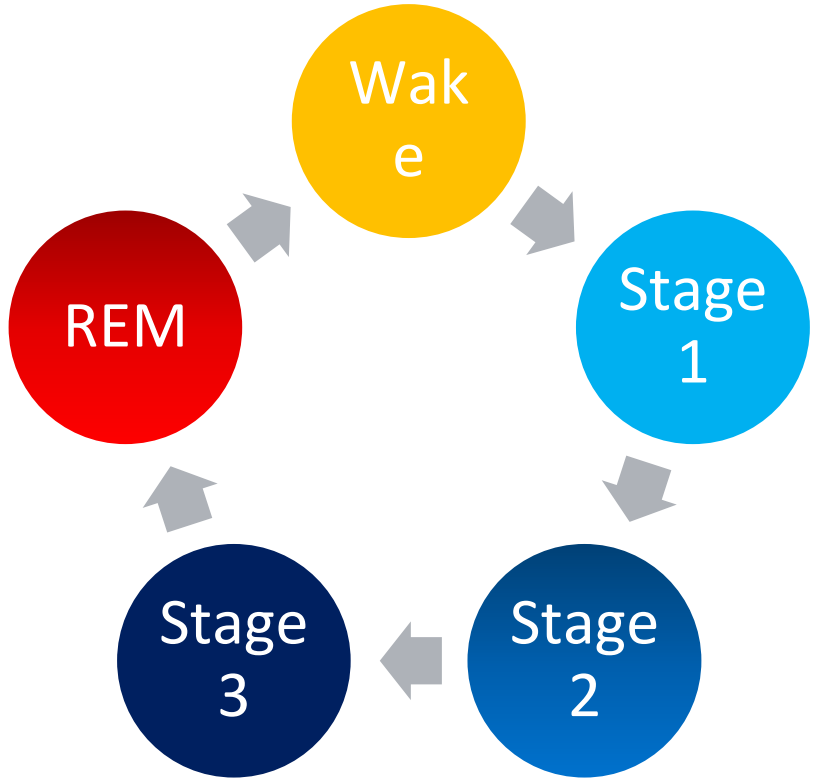
Sleep Cycles

Non-REM Sleep (75%)

- **Stage N1 (<5%)**
  - Light sleep, transition from wake
- **Stage N2 (50%)**
  - Light sleep
  - Decreased muscle tone, heart rate slows, and body temperature decreases
  - Brain waves become slower
- **Stage N3 (20%)**
  - State of deep sleep (hard to wake up)
  - Very slow brain activity
  - No eye movement or muscle activity

REM Sleep (25%) or Stage R

- “Dream state”
- Fast brain waves
- Complete loss of muscle tone

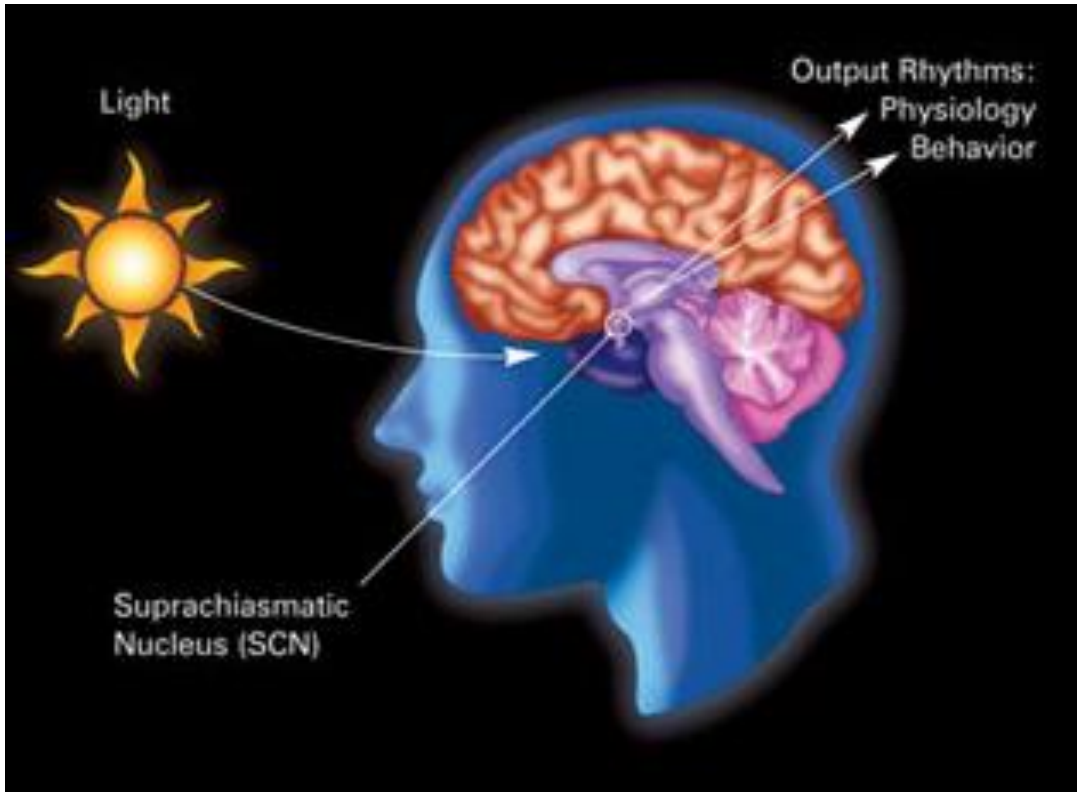


Role of Sleep

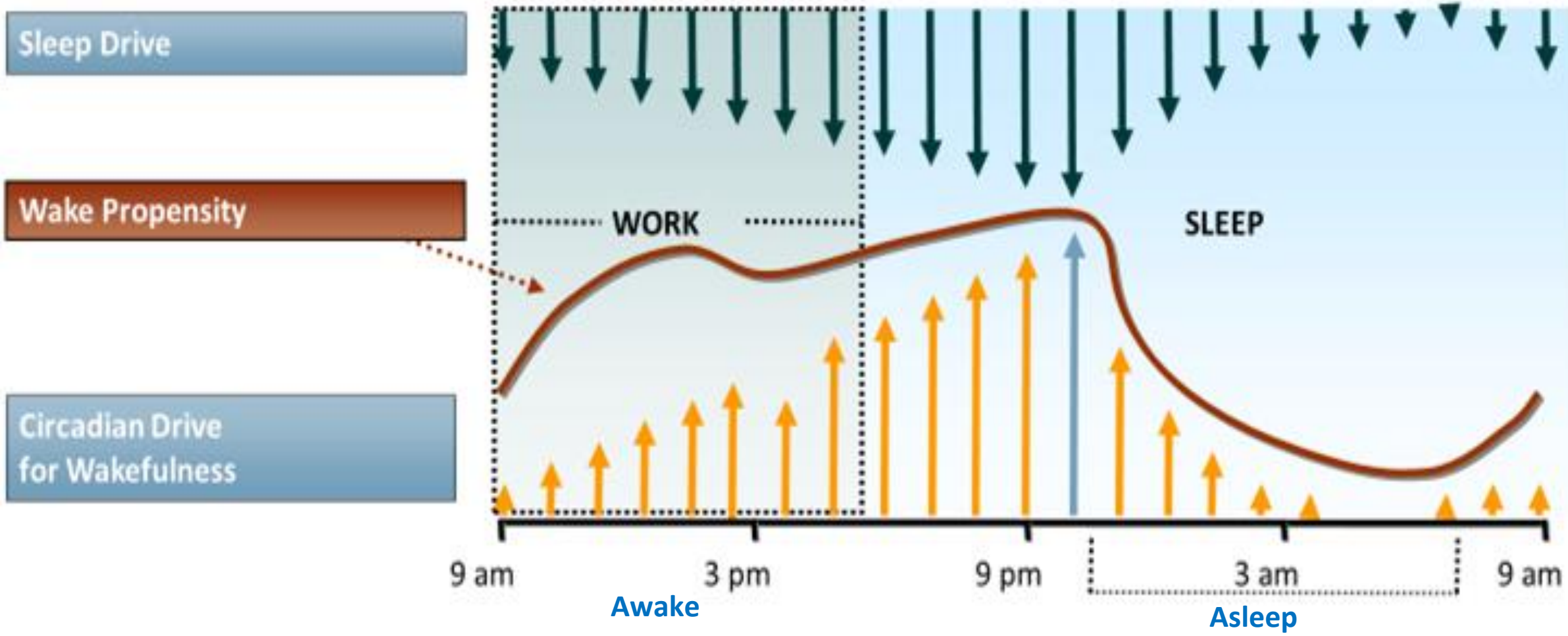
- Physiological restitution and recovery
- Role of Slow Wave Sleep
  - GH secretion, protein synthesis, muscle building & recovery
  - Memory processing
  - Bone growth
  - Immune function
  - Glymphatic system clearance
- Role of REM Sleep
  - Memory consolidation
  - Emotional processing

Sleep Regulation

- Circadian Rhythms
  - > 24 hour (24.2 hours)
- Entraining Agents
  - Light
    - Primary entraining agent
    - Stimulates wakefulness
    - ↓ Melatonin
  - Melatonin
    - Promotes sleep
    - ↑ prior to sleep
- Others:
  - Activities, meals, social cues, ambient temperature.



Sleep-Wake Circadian Cycle



Adapted from: Kryger MH, et al. Principles and Practices of Sleep Medicine. 2000.

Respiratory Physiologic Changes During Sleep

- Diminished mucociliary clearance
  - Absent cough reflex
- Decreased Pulmonary Function
- Ventilatory-Perfusion mismatch
- Hypoventilation

Minute ventilation 0.5-1.5 L

Tidal Volume by 10%

PaO2 - 3-10mmHg

SaO2 - 2%

mPAP - 5 mmHg

Airway resistance

PaCO2 - 2-8 mmHg

Decreased Pulmonary Function During Sleep

- PFTs have a circadian rhythm
- PEFRs and FEV-1 lowest in morning
  - Lowest flow rates btw 2200-0800 (nadir at 0400)
- Contributes to:
  - Nocturnal asthma
  - Decreased exercise performance in the morning
  - COPD worse at night/morning
  - Associated with morning risk of MI

Nocturnal Hypoventilation

- Despite a decrease in energy expenditure, there is an increase in pCO_2 during sleep
- Diminished hypoxic & hypercapnic resp drives
- Decreased central resp drive during sleep
- Decrease minute ventilation and tidal volume
- FRC decreases
- Alveolar ventilation ↓

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Impact of Sleep Disorders & Screening and Treatment of Common Sleep Disorders

Christopher J. Lettieri, MD, FACP, FCCP, FAASM
Professor of Medicine, Uniformed Services University of the Health Sciences
Rockville, MD

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Effect of Sleep on Common Medical Disorders

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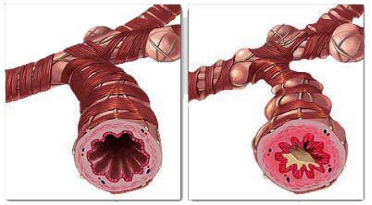
Nocturnal Asthma



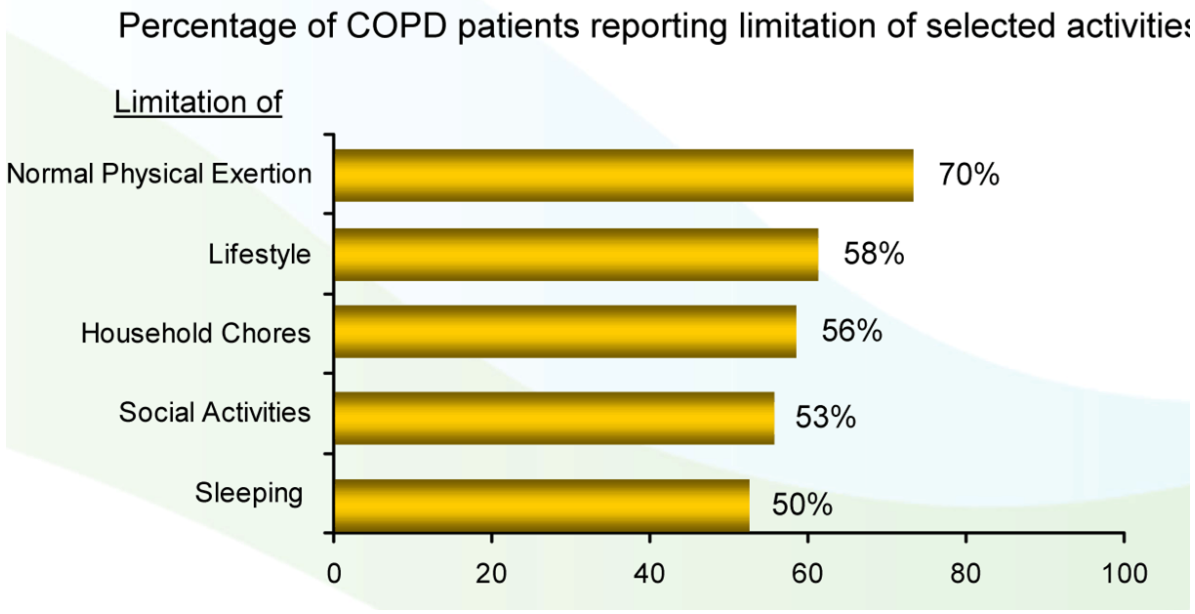
- Nocturnal worsening is a common feature
  - 2/3 experience nocturnal bronchoconstriction
  - Nocturnal symptoms – regard as a dangerous sign
- Asthma-related deaths
  - 28% higher btw 2400-0800 than during the other 16 hours combined
- Circadian biorhythms effect the airways
  - Increase in airway inflammation at night
  - Decrease in pulmonary function/airflow at night
- Both asthma and treatment fragment sleep

CORE *Syndrome*

- **C** Cough Variant Asthma
- **O** OSA
- **R** Rhinitis
- **E** Esophageal Reflux

COPD

- Sleep complaints common in COPD
  - Insomnia (50-70%)
  - Sleep fragmentation
    - ↓ TST, ↑ WASO
- Circadian alterations in PFTs
  - Similar to asthmatics
- ↓ Ventilatory efficiency
- ↑ dead space and ↓ FRC



COPD – Nocturnal Desaturation

- Nocturnal hypoxia common
  - More hypoxemic during sleep than exercise
  - Especially REM
  - 30% with FEV-1 <50% predicted
- Decrease hypoxic and hypercapnic ventilatory response
- Nocturnal hypoventilation
  - Less contribution of diaphragms
- Associated with poor prognosis
  - Mean O2 and O2 nadir directly correlated with survival
- More ventricular ectopy w/nocturnal hypoxia

Chronic Rhinitis

- Sleep fragmentation common
  - Less SWS
- Associations with nocturnal GERD, asthma and OSA
- Two RCT showed nasal steroids improved sleep quality, QoL and daytime sleepiness

Nocturnal GERD

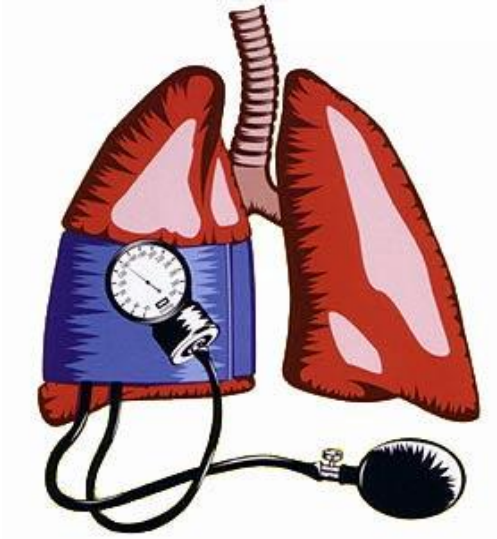
- Common cause of fragmented sleep
- Often “silent”
- GI changes during sleep promote GERD
  - Esophageal sphincter pressure decreases
  - Gastric emptying decreased
  - Gastric acid secretion peaks at 21:00 - 0200
  - Don’t swallow during sleep
    - Prolonged acid contact times

Nocturnal GERD & Asthma

- Nocturnal GERD common with asthma
  - 24% of poorly controlled dz have GERD
  - Acid in distal esophageal
    - causes bronchocontriction
    - decreases PEFRs
    - increases respiratory resistance and increases minute ventilation

Heart Failure

- Sleep quality reported as “poor” in 63%
  - Sleep fragmentation, increased arousals
  - Diminished SWS and REM
- Nocturnal hypoxia
  - Impaired V-Q matching when supine
  - Increased right sided pressure
  - May be associated with CSA
- Diuretics, beta-blockers and statins all shown to fragment sleep and cause EDS



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Impact of Insufficient Sleep

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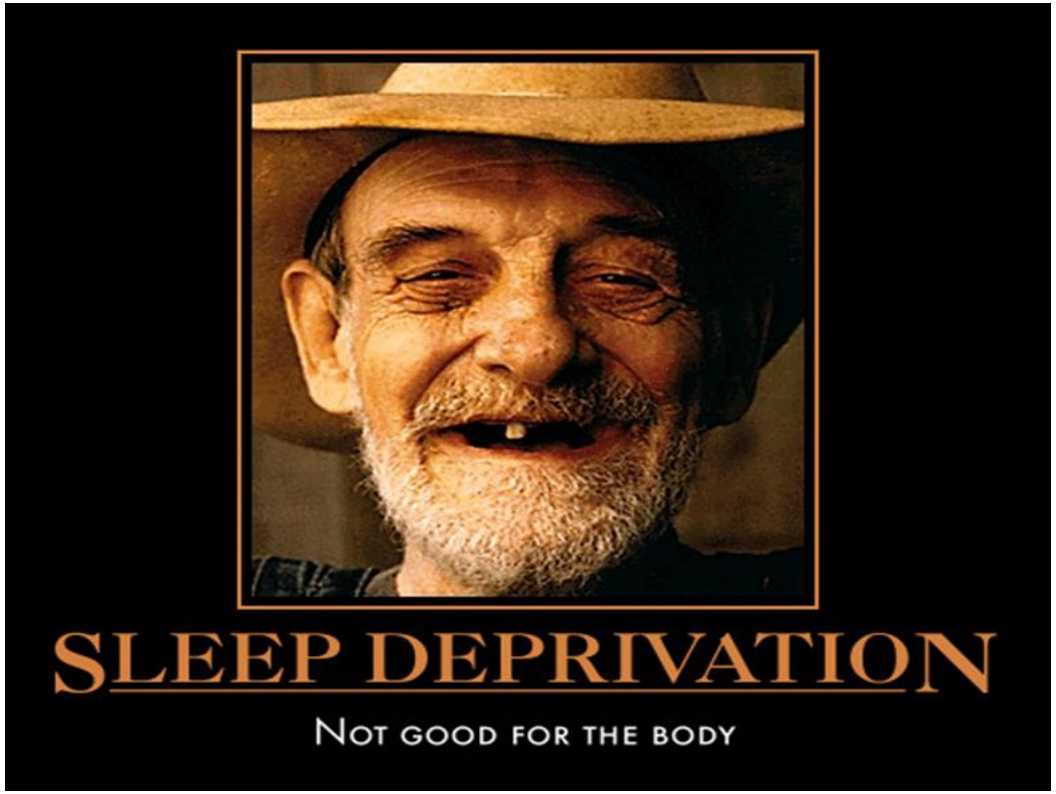
Impact of Insufficient Sleep



Sleepy vs. Excessive Sleepiness

- ***Sleepiness* (somnolence)** – a normal and expected effect mediated by endogenous homeostatic processes, circadian rhythms, metabolic expenditure, and prolonged wakefulness

- ***Excessive Sleepiness* (hypersomnolence)** – pathologic state of inappropriate sleepiness that impairs normal daytime function or results in the inappropriate onset of sleep
  - 30% of American adults

How Much Sleep is Enough?

- Individual Variation
  - Sleep deprived have ↓latency and ↑ sleep drive
- Sleep duration not a true reflection of need
  - tolerance to sleep debt/adenosine
- Physiologic studies of normal adults:
  - 8 hours/night (young adults)
  - 7.5 hours/night (elderly)
- Sleep-Heart Health Study – 7.2 hrs/night
- Sleep Foundation Poll – 7.3 hrs/night

Chest 2008; 134: 653-660
National Sleep Foundation. "Sleep in America" Poll.

Modern Sleep Habits

- Over last 30 years, self-reported sleep duration ↓ **by 1.5 - 2 h** in USA
- 64.4% of adults < 7 h sleep per night
  - 28% < 6 h sleep per night
- >50% of Teenagers obtain < 7h sleep/night
- Mean sleep duration
  - American adults – 6.8 hr/night
  - Military – 6.2 hr/night
  - Urban professionals – 5.8 hr/night
  - Surgical residents – 5.6 hr/night

National Sleep Foundation. “Sleep in America” Poll.

Impact of Chronic Sleep Debt

Neurologic

- Slowed response times
- Narrowing of attention
  - ADD / ADHD
- Diminished executive & cognitive function
- Diminished problem solving
- Impaired moral reasoning
- Decreased situational awareness
- Lower seizure threshold

Behavioral Health

- Irritability
- Depression & Anxiety
- Increased risk of PTSD
- Increased suicidality
- Higher divorce rate
- Lower pain threshold/increased pain response
- Increased substance use & alcoholism
- Decreased QoL

Impact of Chronic Sleep Debt

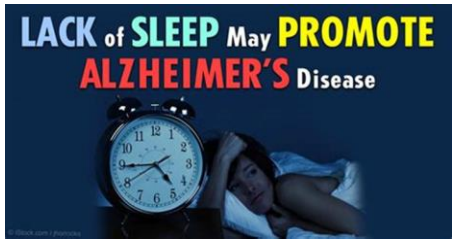
Cardiovascular

- Increase risk for HTN
  - Odds Ratio – 2.2 for <6.5 hrs sleep/night
- Sleep duration independent predictor of MI, CVA, and cardiovascular death
  - Risk greater than DM, smoking, and obesity

Metabolic

- Insulin resistance
- Elevated cortisol
- Increased appetite
- Decreased energy expenditure
- Sleep < 6 hrs/night independent risk for DM and obesity
- <6.5 hrs sleep/night
  - Gain 3-5 lbs more per year compared with >7.5 hrs sleep/night

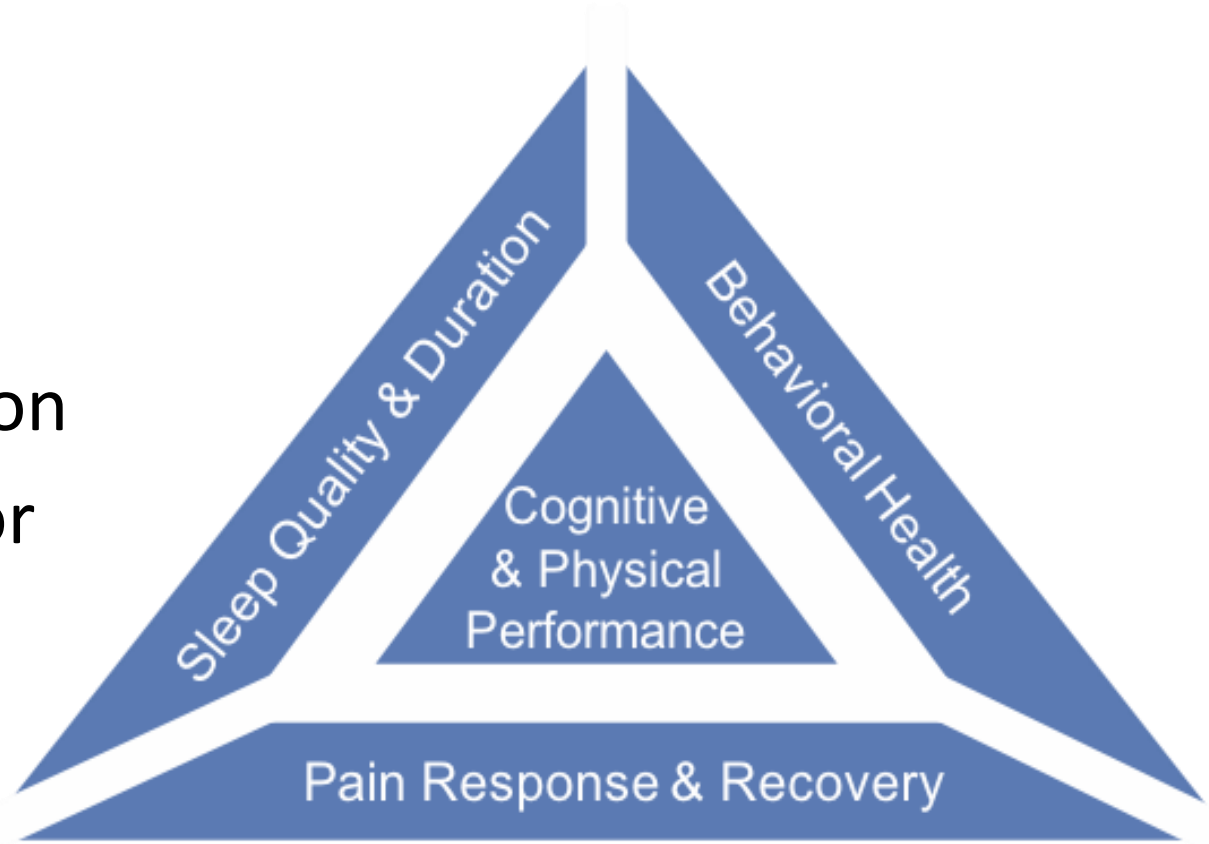
Sleep Debt and Dementia



- Insufficient sleep duration and disrupted sleep architecture associated with increased risk of dementia
  - Near linear association – sleep duration and risk of cognitive decline
- Diminished REM Sleep and prolonged REM latency – strong predictor for developing Alzheimer's
- Insufficient sleep quantity and quality associated with increased beta-amyloid (impaired glymphatic clearance) – precursor for Alzheimer's
- Insufficient sleep leads to increased Tau protein – associated with cellular damage and risk of Alzheimer's

Sleep Quality, Pain, and Behavioral Health

- Interdependent, bi-directional relationship between
  - Chronic pain and BH disorders
  - Sleep debt and chronic pain
  - BH disorders and sleep disruption
- Sleep disorders independent risk for
  - Impaired injury recovery
  - Chronic pain
  - Anxiety, depression, PTSD, and suicidality



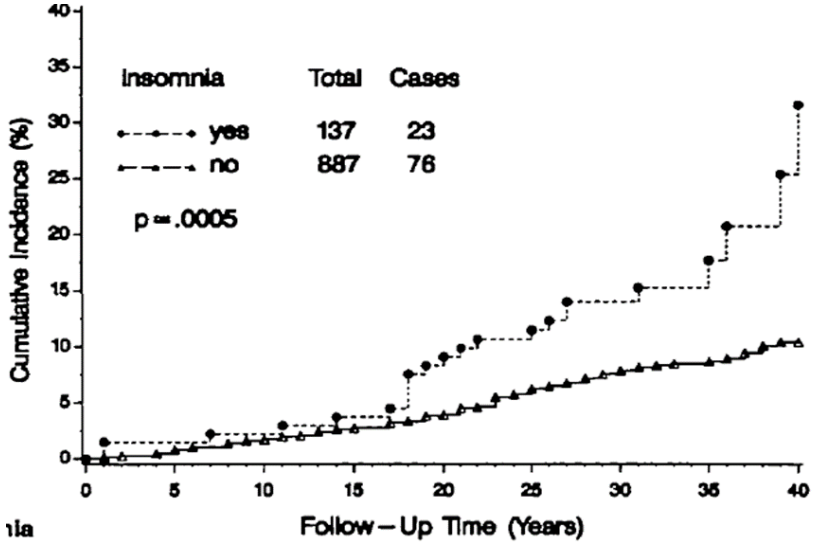
Chronic Pain & Sleep

- Reciprocal relationship between sleep quality/quantity and pain
  - pain disturbs sleep continuity/quality
  - poor sleep further exacerbates pain
- Sleep disturbance - independent and linear correlation w/pain severity after controlling for health and sleep habits
- 70-88% of patients with chronic pain report disturbed sleep
- 42% of short sleepers report chronic pain
- Chronic pain w/ sleep complaints
  - poorer quality of life indices
  - increased healthcare utilization
  - Increased use of Rx pain medications

Smith MT, et al.. J Behav Med 2000
Pilowsky I, et al.. Pain 1985
Drewes AM, et al.. Sleep 1997

Sleep as a Risk Factor for Psychiatric Disorders

- Sleep complaints common with psychiatric disorders
- Psychiatric disorders occur more frequently in those with pre-existing sleep disorders
- Insomnia, OSA and Insufficient sleep all independent risk factors for developing BH disorder
  - Insomnia – OR-2.8 for BH disorder within 3-5 years
  - OSA – OR-1.8 for BH disorder
- Portends worse outcomes
  - Diminished response to treatment
  - Great risk of relapse
  - Higher suicide rates



Chang P., et al. *American Journal of Epidemiology* 1997; 146.2:105-114

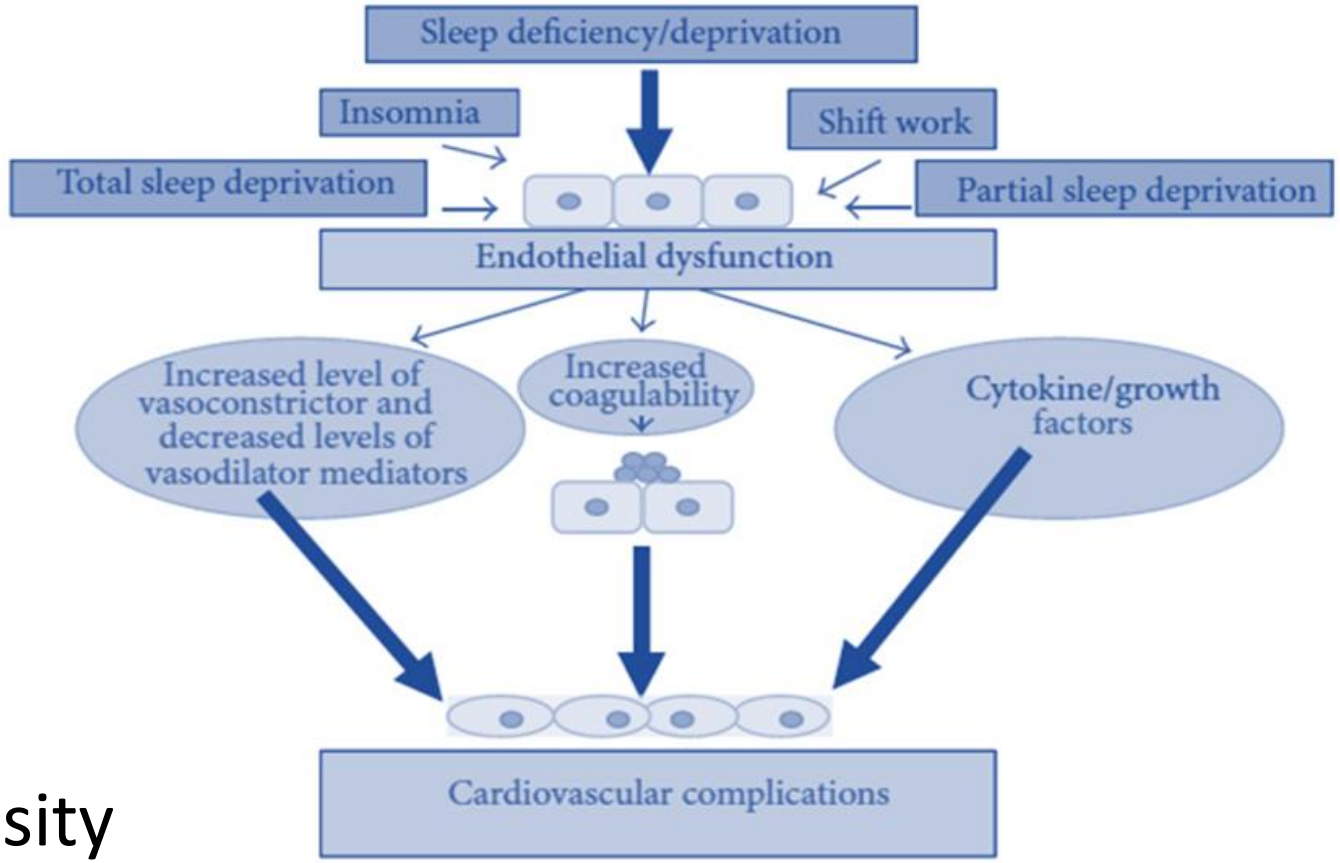
Metabolic Effects of Sleep Loss

- Altered glucose levels
  - Increased insulin secretion
  - Insulin resistance
  - Elevated cortisol
- Increased appetite
  - Imbalance of Leptin and Ghrelin
- Decreased energy expenditure
- Wisconsin Sleep Cohort Study
  - Sleep duration 7.7hrs/night predicted lowest BMI
  - Sleep < 6 hrs/night independently associated with obesity and DM

J Apply Physiol 2005
Chest 2008

Cardiovascular Consequences of Insufficient Sleep

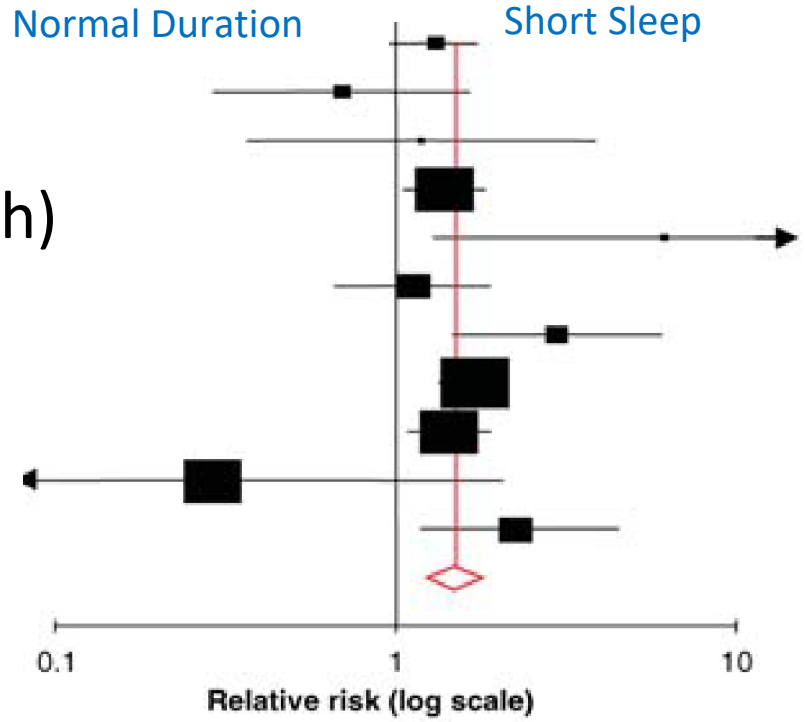
- Strong link between CV disease and Chronic insufficient sleep
  - Pro-inflammatory state
  - Increased autonomic tone
  - Atherothrombotic dysfunction
  - Endothelial dysfunction
  - Impaired fibrinolysis
  - Insulin resistance
  - Weight gain and visceral adiposity



Kohansieh, M, et al. *International Journal of Hypertension* 2015

Insufficient Sleep and Cardiovascular Risk

- Meta-analysis of 15 prospective/longitudinal studies exploring association of sleep duration and cardiovascular outcomes
  - 7-25 years follow-up
  - 474,684 patients, 8 countries
- Compared short (<5-6 h), normal (7-8 h) and long (≥9h) sleepers
- Increased risk of developing or dying of CAD
  - OR 1.48 for short sleepers
  - OR 1.38 for long sleepers
- Increased risk of developing or dying of CVA
  - OR 1.13 for short sleepers
  - OR 1.65 for long sleeper



Cappuccio F et al. *European Heart Journal* 2011; 32.112:1484-1492

Sleep and Mortality

- Nurses Health Study (83,000 subjects)
- Japanese Collaborative Cohort (104,000 subs)
- NHANES NIH Cancer Registry (1.1M subjects)

- Truncated sleep a/w increased all-cause mortality
- U-Shaped association
- 7-8 hours sleep optimal
- < 6 hrs/night = increased risk of death
- > 8 hrs/night also with ↑ mortality

Ferrie JE et al. *SLEEP* 2007; 30.12: 1659-1666

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Insomnia

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Outline

- Understanding Insomnia
  - Defining the condition
  - Prevalence
  - Predisposing and precipitating factors
  - Differentiating Insomnia from poor sleep
- Treating Insomnia
  - Conservative measures and lifestyle modifications
  - Cognitive Behavioral Therapy
  - OTC agents
  - Pharmacotherapy

Why This Matters

- Insomnia reported in 19% of patients evaluated by their primary care provider, only addressed in 7% of cases
- One large multicenter trial of Primary Care providers
  - 8% educated about sleep and healthy sleep habits
  - 6% treated with conservative measures
  - 2% referred for CBT-I
  - 94% prescribed a sedative hypnotic
  - 58% prescribed 2+ medications for insomnia
  - 23% prescribed an anti-psychotic agent
- Data did not account for concomitant OTC use

Prevalence of Insomnia

- Insomnia – most common complaint in general medical practice
- Most common sleep disorder
  - 15-30% have chronic insomnia
  - Increased prevalence with increasing age and co-morbidities
  - 2 times more common among women

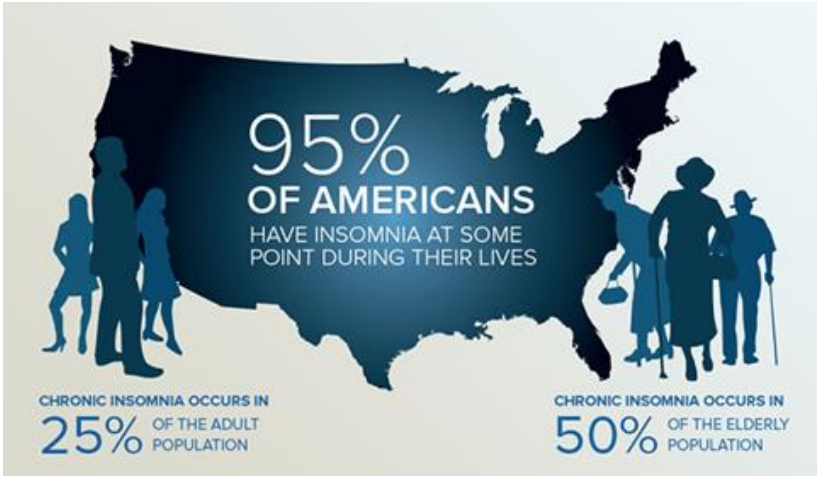
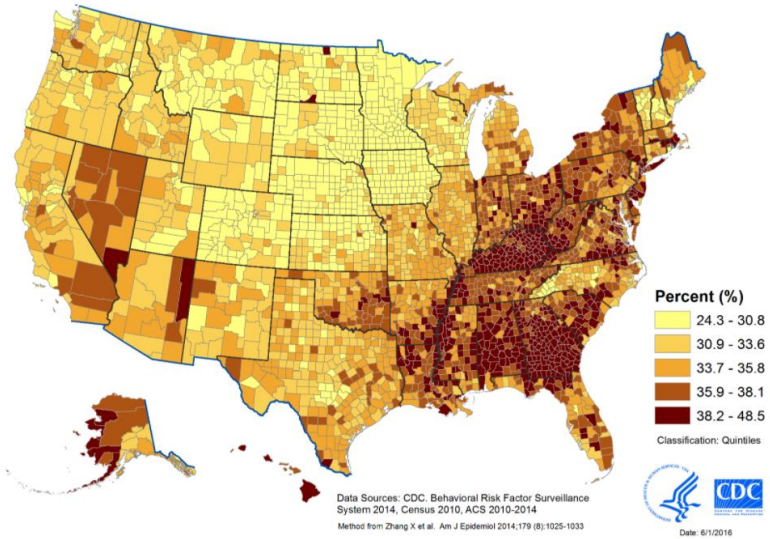


Figure 2. Prevalence of Short Sleep Duration (<7 hours) for Adults Aged ≥ 18 Years, by County, United States, 2014



Dipiro 11th Edition. Chapter 89, Sleep-Wake Disorders

What Is Insomnia?

- Difficulty initiating or maintaining sleep
- Disrupted sleep (frequent awakenings)
- Causes some detrimental effect on daytime function
  - Anxiety, depression, excessive sleepiness
- Occurs on most nights for > 3 month
- Not better explained by another medical or psychiatric condition

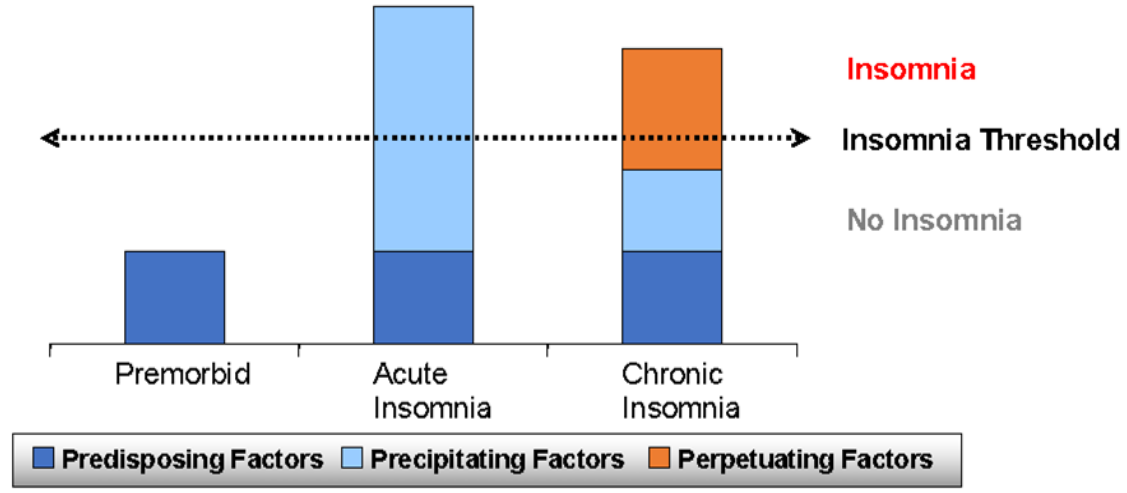
Difficulty falling asleep	*Sleep initiation insomnia*
Difficulty staying asleep	*Sleep maintenance insomnia*
Waking up prior to desired time	*Terminal insomnia*

The International Classification of Sleep Disorders, 3rd Edition (ICSD-3)
Diagnostic and Statistical Manual of Mental Disorders (DSM–5)

The Three P's of Insomnia

Spielman Model of Insomnia

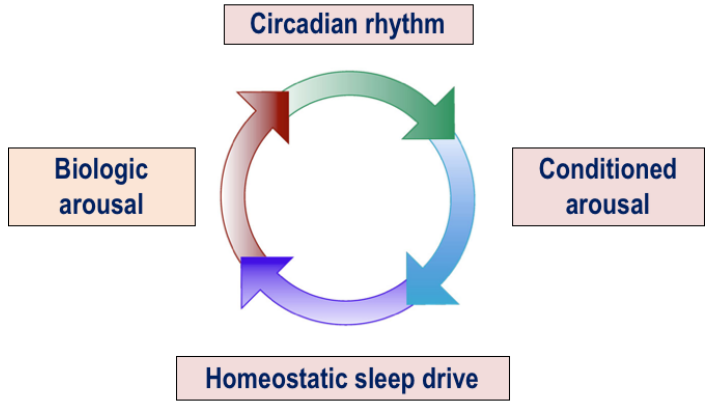
- ***Predisposition***
- ***Precipitant***
  - Life stressor/acute event that can trigger insomnia
- ***Perpetuating***
  - Maladaptive coping strategies that propagate the cycle of insomnia



Adapted from Spielman AJ et al. In: Principles and Practice of Sleep Medicine, 3rd ed. Philadephia: W. B. Saunders Company, 2000.

Perpetuating Insomnia

- Conditioned response that creates sleep-preventing associations, heightened arousal, and anxiety regarding sleep
  - convince themselves they will have insomnia
- Maladaptive strategies adversely effect sleep
  - Insufficient homeostatic sleep drive resulting from naps or sleeping in on weekends
  - Dyssynchronous circadian rhythms from irregular sleep and wake times
  - Wake promoting substances to counter the effects of poor sleep propagates insomnia



Factors That Perpetuate Insomnia
• Excessive time in bed • Irregular timing of retiring and arising • Unpredictability of sleep • Worry over daytime deficits • Multiple bouts (naps, fragmentation) of sleep • Maladaptive conditioning • Increased caffeine consumption • Hypnotic and alcohol ingestion

Spielman A et al. *Psychiatr Clin North Am* 1987; 10.4: 541-553

Insomnia - Treatment

- First make sure it’s insomnia
- Insomnia is chronic (or lifelong) – so is the treatment
- Behavioral modification and positive conditioning – key to success
  - Sleep hygiene
  - Stimulus control
  - Relaxation training
  - Cognitive Behavioral Therapy (CBT)
- Pharmacologic treatments
  - If conservative treatment fails
  - As a bridge to conservative therapy
  - Always for a limited course

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline from the American College of Physicians

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)*

Qaseem A, et al. *Annals of Internal Medicine* 2016; 165.2: 125-133

Behavioral Modification

- **Make sleep a priority**
- Regimented sleep-wake patterns
- Optimize sleep environment
- Avoid (or limit) naps
- Reduce or eliminate alcohol
- Limit use of caffeine and avoid in the afternoon
- Regular exercise
- Limit light exposure in the evenings
- Limit screen time (or at least use the night filter setting)
- Prepare body, mind, and bedroom for sleep

Sleep Hygiene

- **In bed behavior**
  - Avoid TV, internet, e-readers
  - No visible alarm clock display (avoid clock- watching)
- **Sleep Schedule**
  - Maintain a consistent bedtime and wake time 7 days per week
  - Don’t use the Snooze button
- **Caffeine**
  - *Avoid after 2pm*
- **Digital media/ Television**
  - *Limit within 2-4 hours of bedtime*
- **Alcohol**
  - *Avoid within 4 hours of bedtime*
- **Nicotine**
  - *Avoid within 4 hours of bedtime*
- **Exercise**
  - *Not within 3 hours of bedtime*
- **Daytime naps**
  - Avoid daytime naps
- **Light exposure**
  - Minimize bright lights prior to bed

Stimulus Control

- Purpose:
  - Build an association between the Bed and Sleep
  - Break maladaptive, learned associations between the bed and wakeful activities
  - Improve sleep continuity at night
- Rational:
  - Sleep is a behavior susceptible to training
  - *You can re-learn how to sleep well*
- Only use the bed for sleep:
  - Get out of bed if lying awake frustrated; engage in a calming activity
  - Do not get back into bed until you feel sleepy
- Stimulus control for thoughts and emotions
  - Meditation, prayer, simple stretching to relieve stress and prepare for sleep

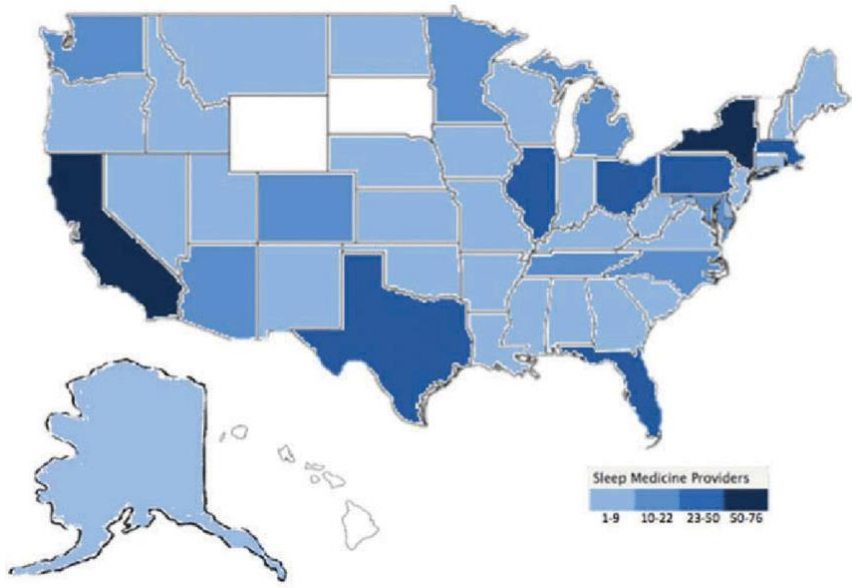
Sleep Restriction & Expansion

- Goal of insomnia therapy – reduce sleep latency, improve sleep efficiency, and resolve negative conditioning
- Sleep restriction/expansion therapy
    1. Establish the goal: an ideal sleep-wake schedule that fits their life/school/work requirements and achieves 8 hours or sleep
    2. Determine when the patient typically falls asleep and when they have to wake up
    3. Consolidate sleep – delay bedtime until after their typical sleep onset time. Keep a fixed Wake time
    4. Once they are able to consistently fall asleep and stay asleep, slowly/incrementally move bedtime towards the goal
- They will not be any more sleep deprived than they already are and it's temporary
- They should continue healthy sleep habits and hygiene

Cognitive Behavioral Therapy for Insomnia – CBT-I

- Strong recommendation (AASM and VA/DoD)
- First-line therapy for chronic insomnia, Reference standard in insomnia treatment
- Combines cognitive therapy strategies with education about
  - Sleep regulation
  - Sleep hygiene
  - Stimulus control instructions
  - Mindfulness and relaxation training
  - Counter-arousal methods
  - Sleep restriction therapy
- Typically 4-8 sessions
- Resource intensive, Limited BSM availability

Behavioral Sleep Medicine Providers



Behavioral and Psychological Treatments for Chronic Insomnia Disorder in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline , 2020

Mobile/Web-based CBT-I

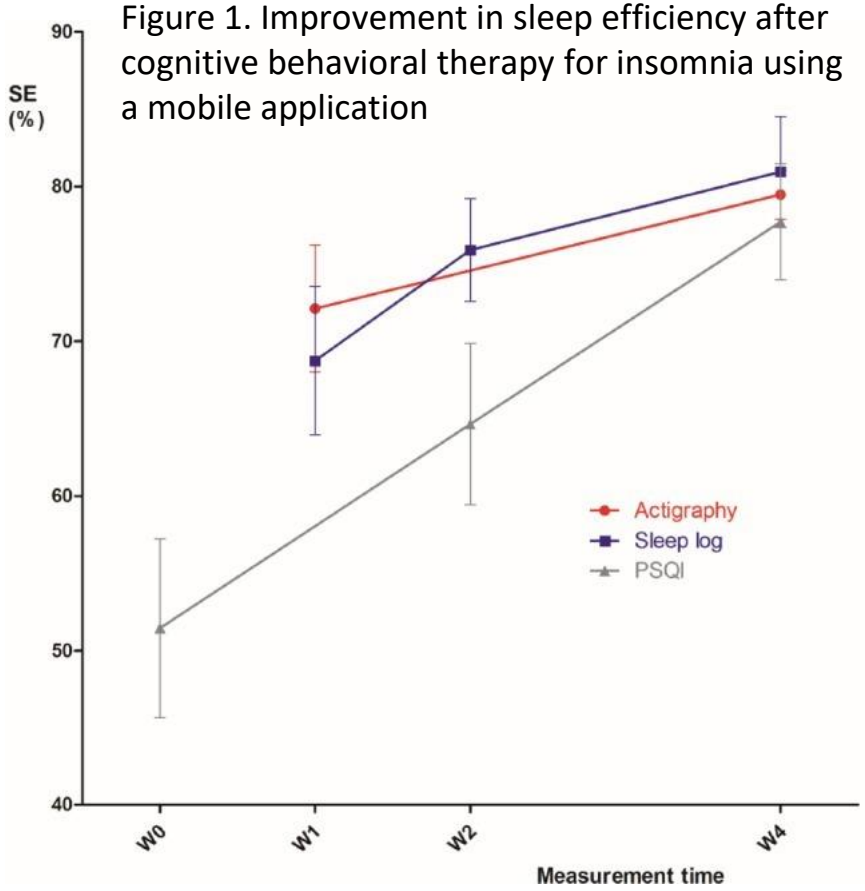
Pros

- Can go at your own pace
- Access whenever you like
- Less resource requirements
- Greater availability

Cons

- Increases screen time
- Limited feedback
- No therapeutic alliance

Figure 1. Improvement in sleep efficiency after cognitive behavioral therapy for insomnia using a mobile application

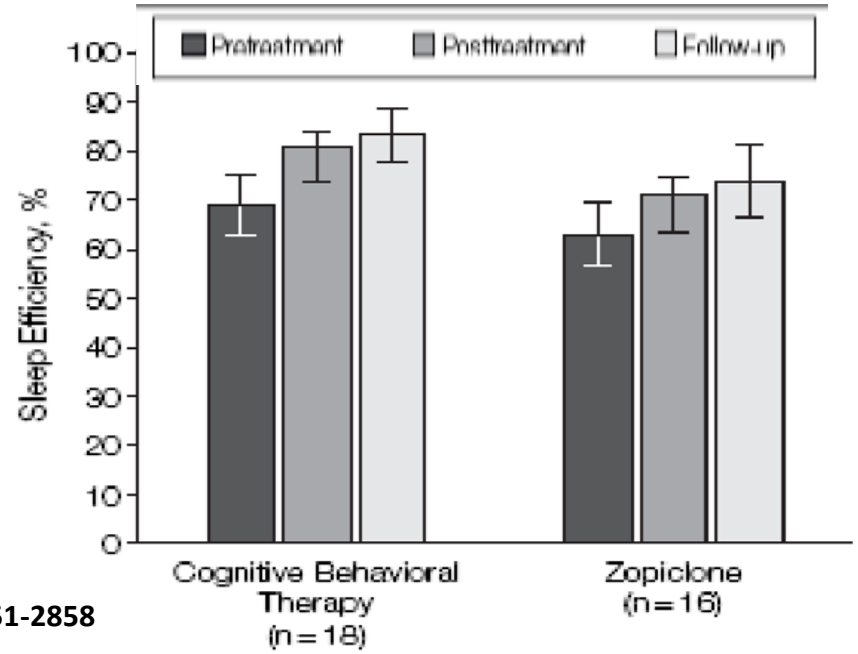


Kang SG et al. *Journal of Clinical Sleep Medicine* 2017; 13.4:633-640

CBT-I vs. Medications

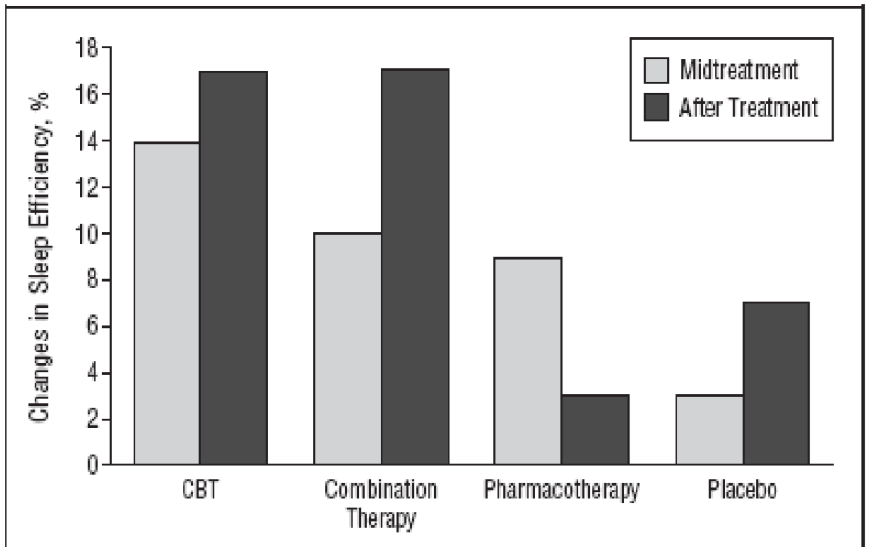
- In head-to-head trials, CBT-I has been consistently shown to be superior to prescription sedative-hypnotics
- Several studies have shown that CBT-I + medications is no more effective than CBT-I alone

CBT-I vs Eszopiclone



JAMA. 2006;295:2851-2858

CBT-I vs Zolpidem



Arch Intern Med. 2004;164:1888-1896

Alcohol

- Alcohol is the most common self-treatment for insomnia
- Improves sleep latency
- Improves sleep continuity, but only in the first half of the night
- Fragmented sleep and early morning awakenings second half of the night
- Disrupts normal sleep architecture
- Non-restorative sleep is common
- Can precipitate other comorbidities (especially OSA)

OTC Sleep Aids

- 24% use OTC sleep aids occasionally,14% use regularly
  - Use increases with increasing age
  - 63% of patients seeking medical attention for insomnia
- Majority contain antihistamines
  - diphenhydramine or doxylamine
- Do not promote normal sleep
  - Can disrupt sleep architecture
- Limited efficacy, which further wanes over time
- Tolerance and psychologic dependence common
- “Hangover effect” common
  - Daytime fatigue and decreased cognitive performance

Gerontologist, 2017; 57:163-170

Melatonin

- Unregulated in the US. Variable efficacy, but relatively safe
- Standard Dosing: 0.3mg – 3mg
  - Chrono-therapeutic, Helps Phase Shift
- High Dosing: >5 mg
  - Soporific effect (Sedating)
  - Risk for adverse phase shifting and daytime somnolence
- High variation in purity and absorption
- If used, I recommend pharmaceutical quality, extended-release formulations

Pharmacologic Therapy

- Sedative-Hypnotics are effective, but have waning effect and unwanted consequences
  - Psychological dependency
  - Impaired daytime function
  - Alterations of normal sleep
  - Does not address cause of insomnia, only treats symptoms
- Should NOT be used as first line therapy
- If used, Rx should be limited to true soporific agents intended for insomnia and used for limited durations

Pharmacologic Therapy - Soporifics

- 4 pharmacodynamic categories based on targeted receptors/neurotransmitter effects on sleep and wake regulation
  - γ-aminobutyric acid (GABA) agonists (promotes sleep)
  - Melatonin receptor agonists (promotes sleep)
  - Histamine antagonists (blocks wake)
  - Orexin (Hypocretin) receptor antagonists (blocks wake)
- Most are Schedule IV controlled substances
  - doxepin and ramelteon not scheduled

Benzodiazepine Receptor Agonists

- Zaleplon, Zolpidem, Eszopiclone
- Most commonly prescribed class
- Relatively effective soporific properties (promotes sleep)
- Targets the GABA-Aα receptor complex
- Some antidepressant and anxiolytic properties (eszopiclone)
- Duration of clinical effect: Zaleplon (1 hr); zolpidem (3 hrs); zolpidem ER (4.5 hrs); eszopiclone (7 hrs)
- FDA Warning(s) and Contraindications – May precipitate complex sleep behaviors (somnambulism, sexsomnia, sleep eating)
- Potential for next day cognitive and physical impairment
- Misuse potential

https://www.fda.gov/news-events/press-announcements/

Melatonin Receptor Agonists

- Ramelteon – only agent in class approved in US
- Tasimelteon approved for non-24 hr sleep-wake disorder
- Melatonin –produced in the pineal gland, levels increase in the dark
- Helps regulate sleep cycling and circadian rhythmicity
- More potent than melatonin, with better pharmacokinetics
- Unscheduled substance, low risk for abuse
- Ramelteon – elimination half-life is 1 to 2.6 hours

Dual Orexin Receptor Antagonists (DORAs)

- Suvorexant; Lemborexant
- Blocks wake promoting neurotransmitter orexin (hypocretin)
- Unique MOA to suppress wake drive (blocks wake)
- Improves sleep onset, sleep efficiency and WASO
- Prolonged elimination half-life (>12 hrs)
  - Can have prolonged clinical duration of effect, especially in the elderly

Sleep, 2013; 36(2):259-267
Neurology, 2012; 79:2265-2274

Doxepin

- Tricyclic antidepressant with anti-histamine properties
  - Histamine H1 receptor antagonist
  - Anti-depressant properties at high dose
  - Pure anti-histamine effect at lower doses approved for insomnia
- Blocks wake/alerting properties of histamine
- 3 or 6mg (usually need 6mg)
  - Off-label 10mg generic tablets often substituted
- Unscheduled substance, low risk for abuse
- Elimination half-life >15 hrs

Off Label Medications Used in Insomnia

- Frequently used as 1st or 2nd line therapy
- Commonly used classes/substances
  - Antidepressants (trazodone, amitriptyline, and mirtazapine)
    - 2nd most common class prescribed for insomnia
  - Anxiolytics (alprazolam and clonazepam)
    - 3rd most commonly prescribed
  - Antipsychotics (quetiapine)
    - 4th most commonly prescribed
  - Antihypertensives (clonidine)

Off Label Medications Used in Insomnia

- Little evidence showing benefits in insomnia
  - Consistent evidence showing potential harm
  - Excessive sedation is a common side effect
  - Often disrupts normal sleep architecture
- Many with relatively long elimination half-lives
- Strong recommendations AGAINST their use solely for insomnia treatment

Trazodone

- Antidepressant with anti-histamine properties
- Commonly used off label for insomnia
- 1/3 – no clinical efficacy
- 1/3 – intolerable side effects
  - Daytime somnolence
  - Sleep fragmentation
  - Priapism (0.05 – 1%)
- AASM - Strongly recommends AGAINST its use

Insomnia Summary

- Insomnia is common and often overlooked in clinic
- First line treatment is CBT-I
- Behavioral modification key to long term success
- Habitual use of OTC agents is generally a bad idea
  - OK for occasional use
- Melatonin is worth trying, but limited effectiveness
- Limit the use and duration of pharmacologic treatments
  - Consider avoiding in the elderly
- Insomnia will persist if they do not have good sleep practices

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Obstructive Sleep Apnea

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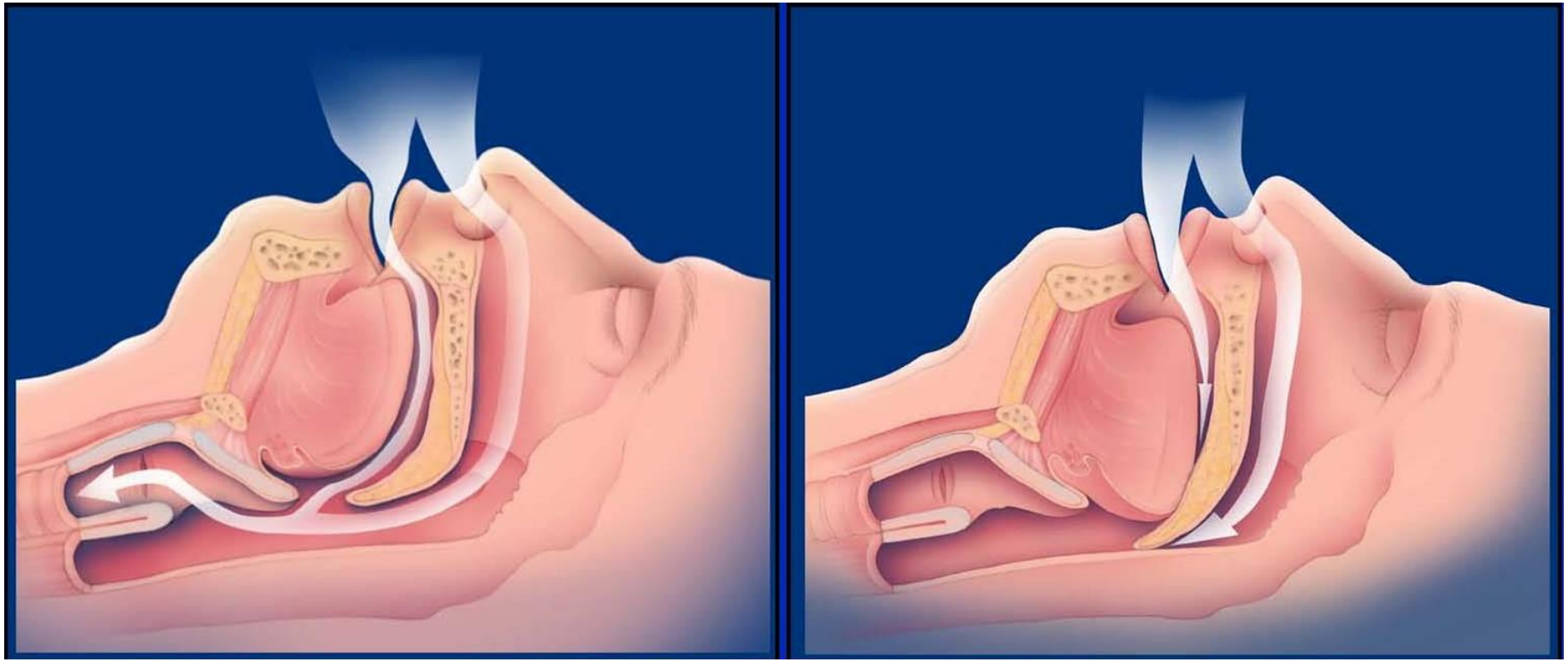
Rockville, MD

OBSTRUCTIVE SLEEP APNEA

Obstructive Sleep Apnea



Normal

Apneic

The International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
Shneerson JM. *Sleep Medicine: A Guide to Sleep and Its Disorders*. 2nd ed. Malden, MA: Blackwell Science Ltd; 2005.

Obstructive Sleep Apnea

- Recurrent airway obstruction during sleep
  - Subluxation of the oropharynx
- Sleep fragmentation
  - Abnormal sleep architecture
- Intermittent hypoxia
  - Endothelial dysfunction
  - Elevated catecholamine tone

Physiologic Effects of OSA

- Apneas are not the problem
- Detrimental effects of OSA related to:
  - Recurrent upper airway obstruction
    - Ineffective ventilation
    - Resulting hypoxia/hypoxemia
  - Disrupted sleep architecture
    - Non-restorative sleep
  - Repetitive arousals
    - Increased catecholamine tone
    - Endothelial dysfunction

Epidemiology

- 18-24% of Americans
  - 1 in 5 adults with at least mild OSA
  - 1 in 15 adults with at least moderate OSA
  - 48% of CHF admissions
  - 60% of CVA admissions
  - 72% of elderly in long-term care
- OSA is largely under diagnosed
  - Less than 5% receiving treatment
  - Diagnostic profiling
  - Lack of knowledge among PCMs

OSA: High-Risk Features

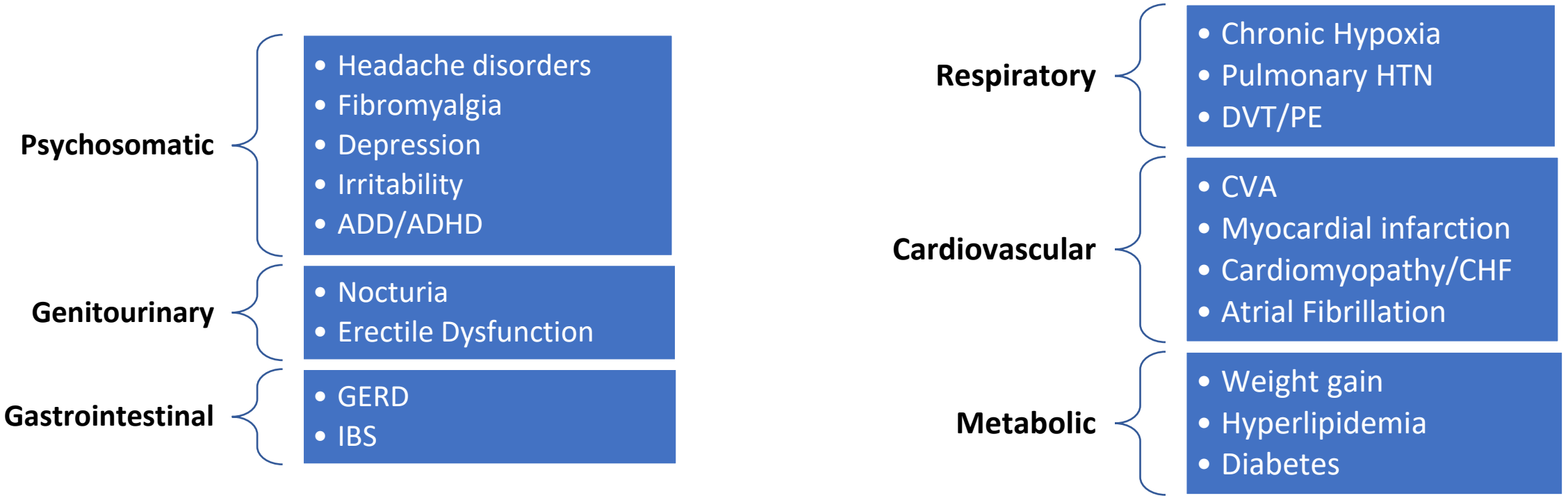
- Habitual snoring
- Daytime somnolence or fatigue
- Witnessed apneas
- Restless or non-refreshing sleep
- Overweight, recent weight gain
- GERD, HTN, DM, Metabolic syndrome
- Erectile dysfunction
- Depression
- Sweating and dry mouth at night
- Nocturia
- Retro/micrognathia
- Hypothyroidism

OSA Screening

STOP BANG

- S Snoring
- T Tired
- O Observed Apnea
- P Pressure-HTN
- B BMI > 30
- A Age > 50
- N Neck > 17”
- G Gender (M)

Proven Associations with OSA

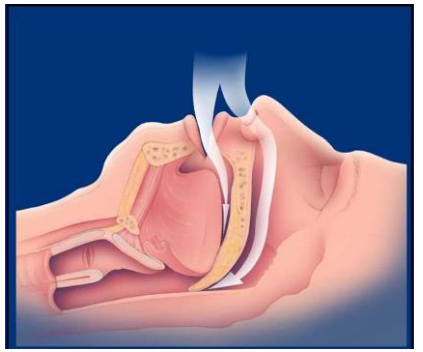


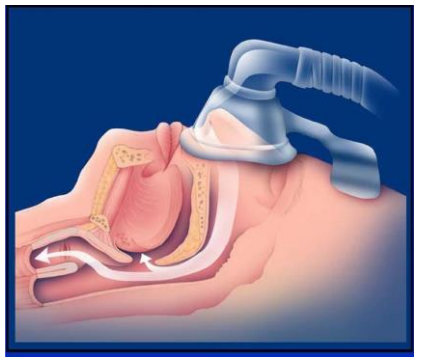
Treatment Options

- Conservative
  - Weight Reduction
  - Positional Therapy
- CPAP
- Oral Appliance
- Surgery
- Hypoglossal nerve stimulation

Positive Airway Pressure

- Non-invasive mechanical airway support
- Pressure column of to “stent” upper airways
- Most effective therapy for OSA
- Limited by tolerability and compliance
  - 40-45% compliance rate in most studies
  - ~80% with proper counseling/follow-up
  - Reality: <1/4th of those diagnosed with OSA use CPAP regularly





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Willis Ekbom Disease
"Restless Legs Syndrome"

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Restless Legs Syndrome

- Common, often under recognized and difficult to treat condition
- Prevalence – 5-10% of Adults
- Can be mistaken for insomnia as it can prevent sleep onset
- Clinical diagnosis based on presence of 4 cardinal symptoms

Restless Legs Syndrome

4 Cardinal Features
1. Unpleasant sensation • Typically in the legs, but can affect arms and lower back 2. Urge to move, improves with movement 3. Occurs or worsens with rest/immobility • Prolonged car ride or flight 4. Circadian timing – worse in evening/night

URGE

- **Urge to Move**
- **Rest worsens symptoms**
- **Gets better with activity**
- **Evening/night worsening**

RLS - Epidemiology

- Typical age of presentation: 40-50 years old
  - Prevalence increases with increasing age
  - Earlier onset in familial forms
- More common in women (2:1 F:M ratio)
- Different prevalence in different ethnicities/geographical regions
  - 5-10% (U.S. and Northern Europe)
  - 3% (Mediterranean/Middle Eastern)
  - 1-5% (Eastern Asia)
  - Uncommon in African Americans

RLS Associations

- Iron deficiency (Ferritin < 50)
- Diabetes Mellitus
- Peripheral Vascular Disease
- Venous insufficiency
- Parkinson’s Disease
- Chronic Kidney Disease (end stage renal disease)
- Obstructive Sleep Apnea
- Antidepressants
- Pregnancy (3rd trimester)

RLS Treatment

- Iron replacement when needed
- Dopaminergic Agents
- Gabapentin/Pregabalin
- Benzodiazepines
- Narcotics
- Non-pharmacologic therapies

THANK YOU

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American Academy of Cardiovascular Sleep Medicine (AACSM)

The source for Information & News on Cardiovascular Sleep Medicine

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Narcolepsy

Lee A. Surkin, MD, FACC, FCCP, FASNC, FAASM
Founder, American Academy of Cardiovascular Sleep Medicine
President, Empire Sleep Medicine

Narcolepsy Diagnostic Criteria
International Classification of Sleep Disorders

- **Narcolepsy Type 1**
  - Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥ 3 months
  - The presence of 1 or both of the following:
    - Cataplexy
    - MSLT: Mean sleep latency of ≤8 minutes and ≥2 sleep-onset REM periods (SOREMPs). A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT.
    - CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay.
- **Narcolepsy Type 2**
  - Cataplexy is absent
  - Hypocretin levels low normal to normal

International Classification of Sleep Disorders – Third Edition (ICSD-3). (2014) American Academy of Sleep Medicine

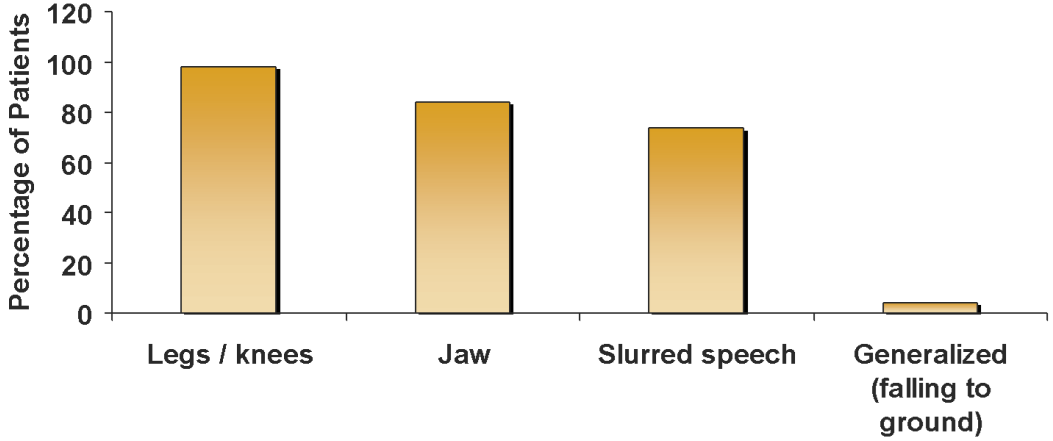
Signs and Symptoms

- Diagnostic delay ≥10 years; may be associated with misdiagnosis
- Economic and medical burden is very high
- Symptoms include:
  - Cataplexy (type 1 only)
  - Excessive daytime sleepiness (EDS)
  - Fragmented sleep
  - Sleep paralysis
  - Hallucinations
  - Vivid and frequent dreaming
  - Automatic behaviors

Thorpy MJ, Hiller G. *Am Health Drug Benefits*. 2017;10(5):233-241.

Cataplexy

- Muscle weakness triggered by emotions
  - Joking, laughter, excitement, anger
  - Brief duration, mostly bilateral
- May affect any voluntary muscle
  - Knee / leg buckling, jaw sagging, head drooping, postural collapse
- Consciousness maintained at start



International Classification of Sleep Disorders – Third Edition (ICSD-3). (2014) American Academy of Sleep Medicine

Anic-Labat 1999

Narcolepsy – Associated Features

- Sleep paralysis
  - Sudden inability to move on falling asleep or on awakening
  - Episodes are generally brief and benign, end spontaneously
- Hallucinations
  - Vivid hallucinations at sleep onset (hypnagogic) or awakening (hypnopompic)
  - Auditory or visual
- Headaches
- Depression

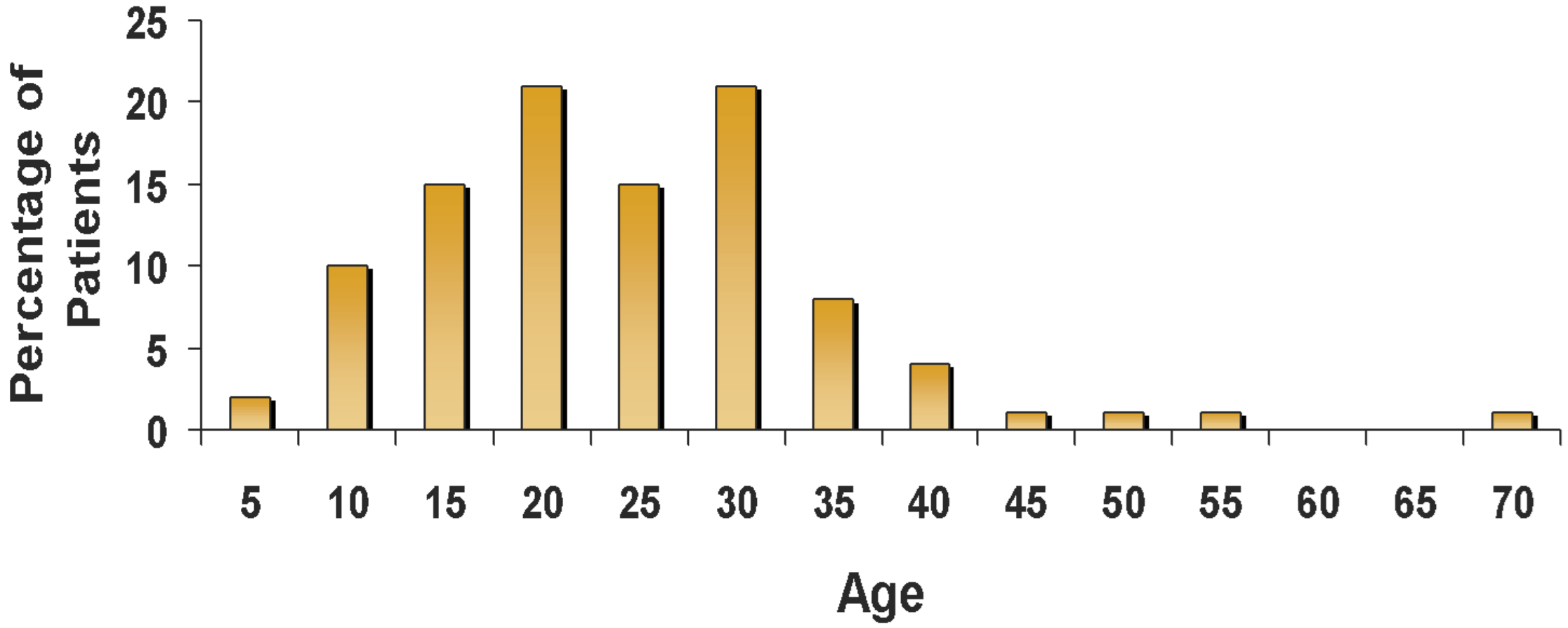
International Classification of Sleep Disorders – Third Edition (ICSD-3). (2014) American Academy of Sleep Medicine

Prevalence

- Worldwide estimates approximately 20–55/100,000
- US Health Care Claims Database, 2008-2010:
  - Prevalence overall: 79.4/100,000
  - Regional data prevalence and incidence:
    - North Central US – highest
    - Western US – lowest
- Incidence of narcolepsy without cataplexy significantly greater than narcolepsy with cataplexy
- ~50% greater incidence in women across most age groups
- Prevalence highest in 21-30 years age group
    - Median age of onset 16 years

Scheer D, Schwartz SW et al. *Sleep*. 2019;42(7)

Narcolepsy – Age of Onset

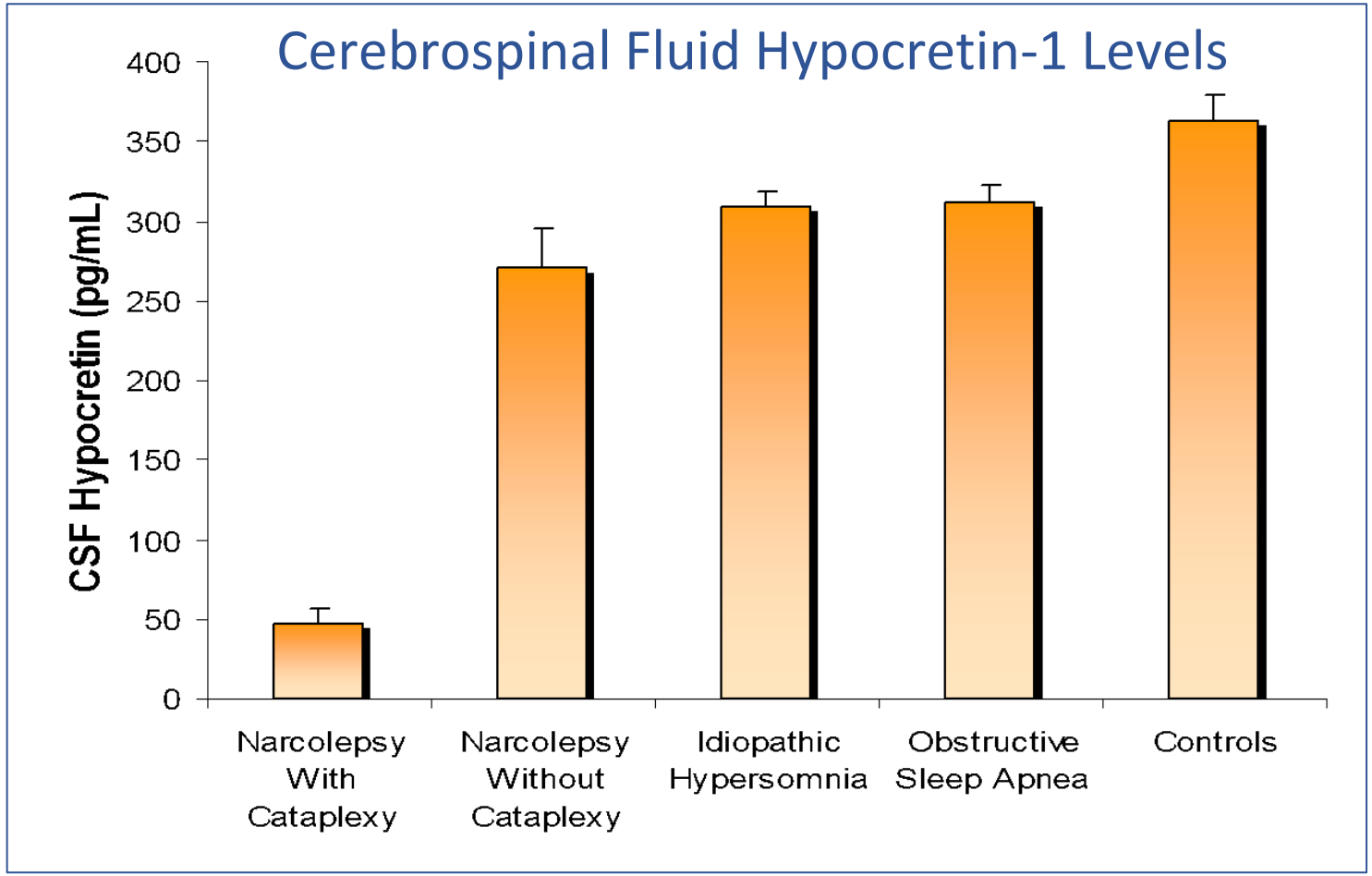


Parkes 1985

Narcolepsy – Pathophysiology

Hypocretin deficiency

- ~90% of orexin-producing neurons are lost in human narcolepsy with cataplexy

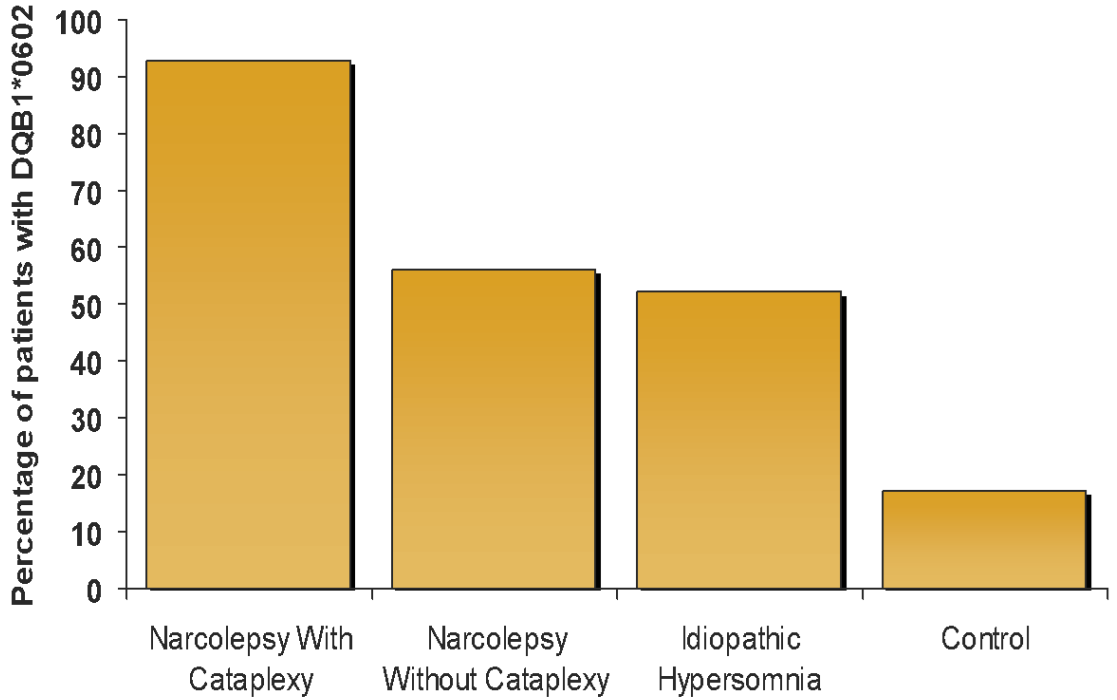


Mignot et al 2002

HLA-Narcolepsy Association

Autoimmune hypothesis

- HLA linked to many autoimmune diseases, and narcolepsy has the strongest known HLA association
- HLA-DR2 and DQB1*0602 are tightly associated with narcolepsy with cataplexy, as is multiple sclerosis
- HLA DQB1*0602 is found in ~90% of patients with type 1 narcolepsy
- Carrying this gene increases narcolepsy risk ~200-fold



HLA DQB1*0602

Scammell, TA. *N Engl J Med* 2015; 373:2654-2662

Therapeutic Approaches

- Pharmacotherapy
  - Wake Promoting agents
  - Reduction in Cataplexy
  - Improved sleep continuity
- Behavioral interventions
  - Napping, optimizing sleep-wake cycle
  - Avoidance of cataplectic triggers
- Psychosocial and educational interventions

Narcolepsy and Cardiovascular Disease

Orexin Receptors: Cardiac and Central

- Orexin A and B, and Orexin receptors 1 and 2 present throughout the rat myocardium and centrally[1]
- Exert a central effect in increasing HR and BP[2]
- Orexin and Orexin 1 receptor-containing nerve fibers have been identified in the paraventricular nucleus (central site for integration of sympathetic outflow and cardiovascular function)
- Orexin A activates both Orexin 1 and 2 receptors
- Orexin B activates Orexin 2 receptors

1. Patel, V et al. *Clin Sci* 2018 Dec 132: 2547-64;
2. Shivasaka, T et al. *Am J Physiol* 1999; 277(6): R1780-5

Orexin Receptors: Cardiac and Cardiac-Hemodynamic Effects

- Only Orexin B effects myocardial contractile shortening[1]
- Orexin B shown to be cardioprotective after ischemia/reperfusion[1]
- Humans with CHF demonstrate a negative correlation between Orexin B receptors and heart failure severity[1]
- Sleep related changes in BP are blunted in mice lacking orexin[2]
- HR in NT1 more variable during wake and normal to high during sleep
  - Arousals lead to a blunted heart rate response[3]
- Arousal related ↑ in HR: controls >NT2 > NT1[4]

Patel, V et al *Clin Sci* 2018 Dec 132: 2547-64; 2. Bastianini, S et al. *Sleep* 2011; 34(2): 213-8; 3. Fronczek, R et al. *Sleep* 2017; 36(1): 9-10; 4. Sorenson, GL et al. *Sleep* 2013; 36(1); 91-8

Orexin Loss: Link to Sleep Fragmentation and Endothelial Dysfunction

- Endothelial dysfunction is induced by chronic sleep fragmentation[1]
- Apo E knockout mice (prone to atherosclerosis) when subjected to sleep fragmentation produce less orexin and develop larger atherosclerotic lesions[2]
  - Administering orexin ↓ sleep fragmentation and atherosclerosis severity
- Mice deficient in Orexin receptor 2 with Narcolepsy phenotype have ↑ cardiac dysfunction and myocardial scarring[3]
- Sleep fragmentation causes orexin deficiency and NT1 is an orexin deficiency disorder suggesting a bidirectional relationship

1. Carreras, A et al. *Sleep* 2014; 37(11): 1817-24; 2. McAlpine, CS et al. *Nature* 2019; 566(7744): 383-7; 3. Perez, MV et al. *J Am Coll Cardiol* 2015; 66(22): 2522-33

Orexin Loss: Extra-Cardiac Implications

- Sleep fragmentation decrease in orexin also discovered in bone marrow[1]
- Increased pre-neutrophils results in an ↑ in CSF1 → WBC production → atherosclerosis
- CSF1 also has a direct effect on arterial wall
- Orexin deficiency is associated with reduced leptin signaling in mice with sleep fragmentation[2]
  - Associated with ↑ WBC production in mice
  - Suggests a metabolic contribution

CSF1 = colony stimulating factor-1

1. McAlpine, CS et al. Nature 2019; 566(7744): 329-30;
2. Nagaretty PR et al. *Cell Metab* 2014(19): 821-35

Blunted Nocturnal Blood Pressure Dipping (Non-Dipping)

- Defined as a <10% decrease in BP during sleep
- Associated with increased CV mortality and morbidity, independent of BP and CV risk factors[1] and CHF[2]
- More common in narcolepsy vs. controls
  - 31% vs 3% (p=0.002)[3]
  - Consistent when controlling for sympathetic activity in NREM sleep[4]
  - Associated with increased sleep fragmentation, arousals, PLMS and PLMS with arousals[5]

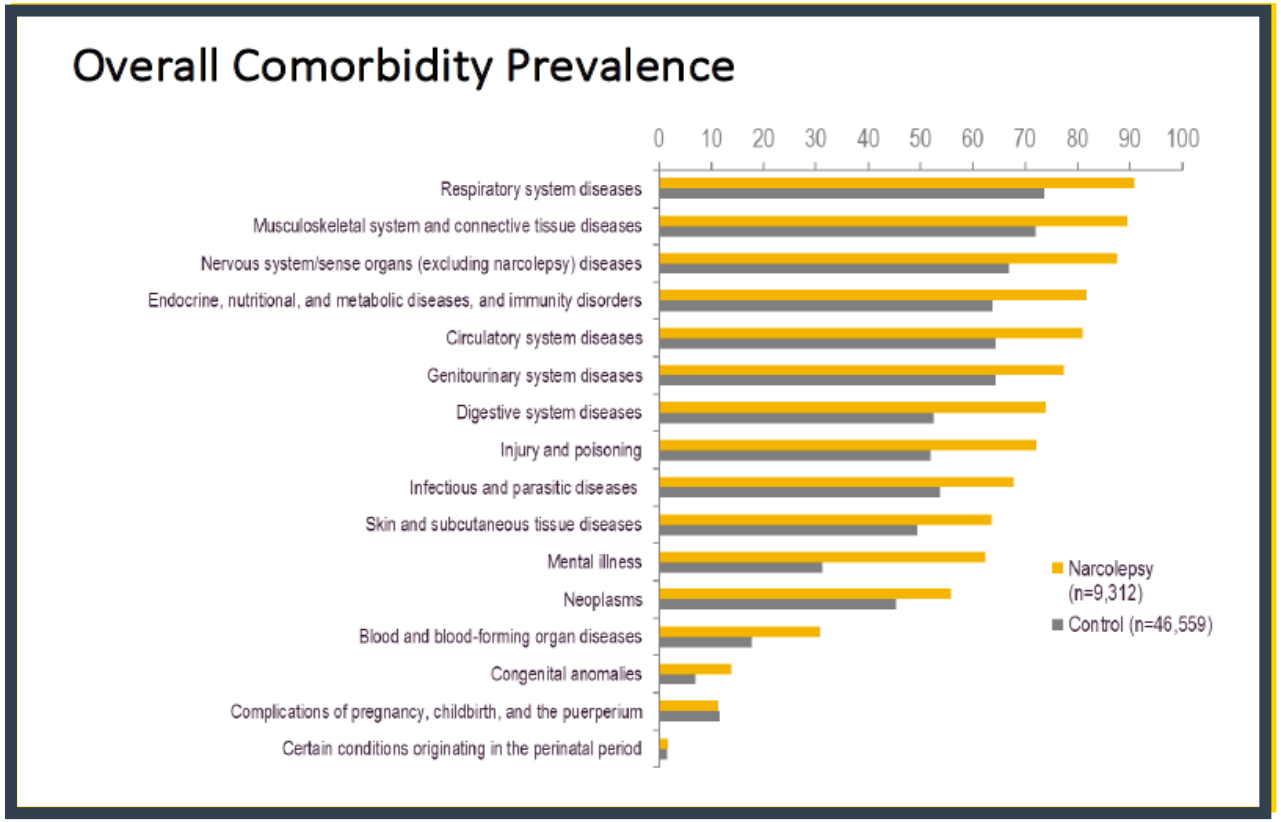
1. Sega R. et al. *Circulation* 2005; 111: 1777-83; 2. Ingelsson, E et al. *JAMA* 2006; 295: 2859-66; 3. Dauvilleirs, Y et al. *PLoS One* 2012; 7(6): e38977; 4. Donadio, V et al. Sleep Med 2014; 15(3): 315-21; 5. Grimaldi, D et al. *Sleep* 2012; 35(4): 519-28

Narcolepsy and CV Risk: Bond Study

- Retrospective study: 5-year US claims data 2006-2010
- 55,871 adults >18yo, 9,312 with NT1 or NT2 and matched controls

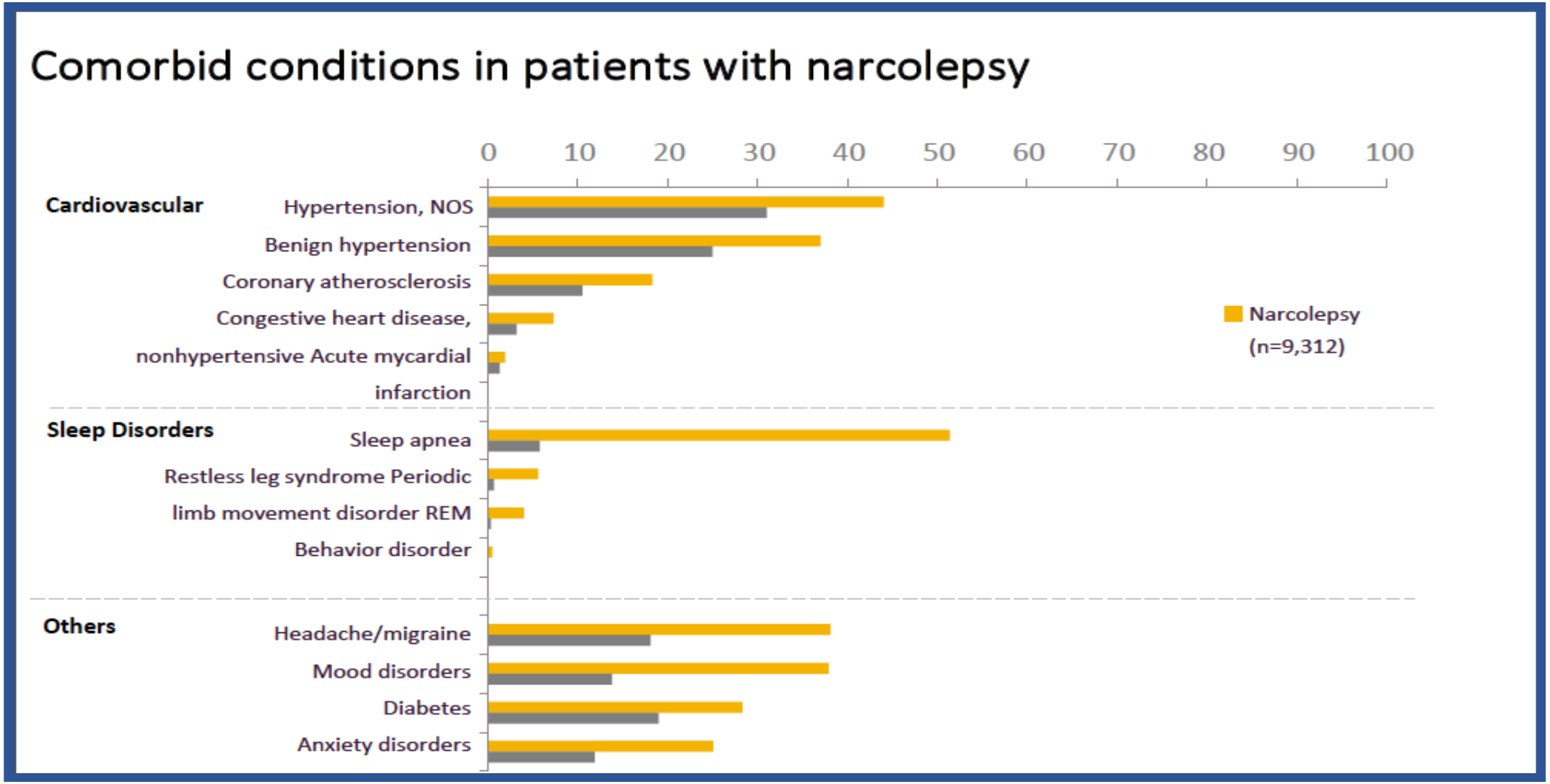
Results:

- CVA risk OR: 2.5
- MI risk OR: 1.6
- Cardiac arrest OR: 1.6
- Coronary revascularization OR: 1.7



Black J, Reaven NH, Funk SE, et al. *Sleep Medicine* 2017;33:15.

Narcolepsy and CV Risk: Bond Study



Cardiometabolic Comorbidities in Narcolepsy

- Arterial hypertension (17%)
- Ischemic heart disease (8%)
- Dyslipidemia (18%)
- Diabetes Mellitus Type 2 (10%)
- Cardiac arrhythmia/atrial fibrillation (5%)

Feketeova E, Tormasiova M, et al. *Sleep Med.* 2020;67:15-22.

Obesity and Narcolepsy

- Obesity is common in adults and children with narcolepsy and is a significant risk factor for cardiovascular disorders
- Obesity can predispose to cardiometabolic abnormalities and OSA
- Obesity is most obvious in children and occurs at time of onset of narcolepsy
  - Precocious puberty occurs more commonly and should be looked for

Nordstrand SEH, Juvodden HT, Viste R, et al. *Sleep.* 2019.

Therapeutics and Narcolepsy: Alerting Medications for EDS

Medication	Mechanism of action
Caffeine[1]	Adenosine receptor antagonist
Methylphenidate[2]*, amphetamines[3]*	Sympathomimetic; enhance neurotransmission of dopamine, norepinephrine, serotonin
Modafinil[4]*, armodafinil[5]*	Dopamine reuptake inhibitor
Sodium and Low-Sodium Oxybate[6,7]*	$GABA_B$ agonist
Solriamfetol[8]*	Dopamine-norepinephrine reuptake inhibitor
Pitolisant[9]*	Histamine H_3 antagonist/inverse agonist
Reboxetine[10]†	Selective norepinephrine reuptake inhibitor
TAK-944/925[11]†	Orexin 2 receptor agonist

*FDA approved to treat excessive sleepiness associated with narcolepsy; †Investigational; not FDA-approved for any indication. GABA = gamma-aminobutyric acid

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Therapeutics for Narcolepsy: Alerting Medications for EDS

Intervention	Recommendation	Excessive daytime sleepiness	Cataplexy	Disease severity	Quality of life
Modafinil	Strong	×		×	×
Pitolisant	Strong	×	×	×	
Sodium oxybate	Strong	×	×	×	
Solriamfetol	Strong	×		×	×
Armodafinil	Conditional	×		×	
Dextroamphetamine	Conditional	×	×		
Methylphenidate	Conditional	×		×	

Maski K et al, JCSM, 2021, https://doi.org/ 10.5664/jcsm.9328; Morgenthaler TI, et al. *Sleep*. 2007;30:1705-1711.

Agents Under Investigation

New form of sodium oxybate

- Once-a-night formulation

Modafinil augmentation

- Modafinil/flecainide (THN102)

GABA-A antagonists

- Clarithromycin
- Flumazenil
- Pentetrazol (BTD-001)

Norepinephrine reuptake inhibitor (NRI)

- Reboxetine

H3R inverse agonist

- SUVN-G3031

Orexin agonists

- TAK-925/944

Sympathomimetic amine

- Mazindol