Insomnia and aging: Risks for brain health and new treatment approaches

Daniel J. Buysse, MD

UPMC Professor of Sleep Medicine
Professor of Psychiatry and Clinical and Translational Science
University of Pittsburgh School of Medicine

buyssedj@upmc.edu

Sleep, Circadian Rhythms, and Aging: New Avenues for Improving Brain Health, Physical Health and Functioning

North Bethesda, MD

October 4-6, 2015

Disclosures

- Current funding: NIA, NHLBI, NIA, NCATS, AHRQ, NIGMS, American Sleep Medicine Foundation
- Other financial relationships and potential conflicts of interest

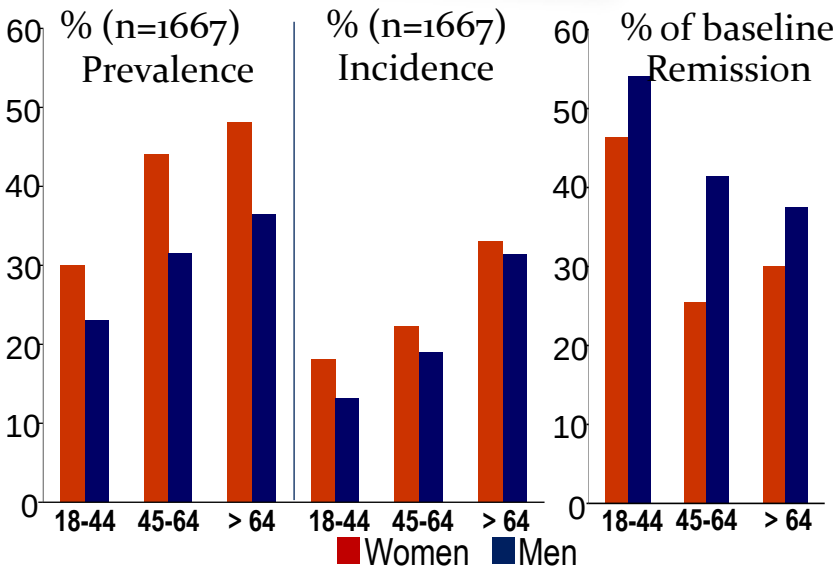
Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	None
Consultant	Web MD, CME Outfitters, Medscape, Emmi Solutions, Merck, Philips Respironics, Eisai, Purdue Pharma
Speakers' Bureaus	None
Financial support	None
Other	Paid speaker at educational conferences: Astellas, Servier

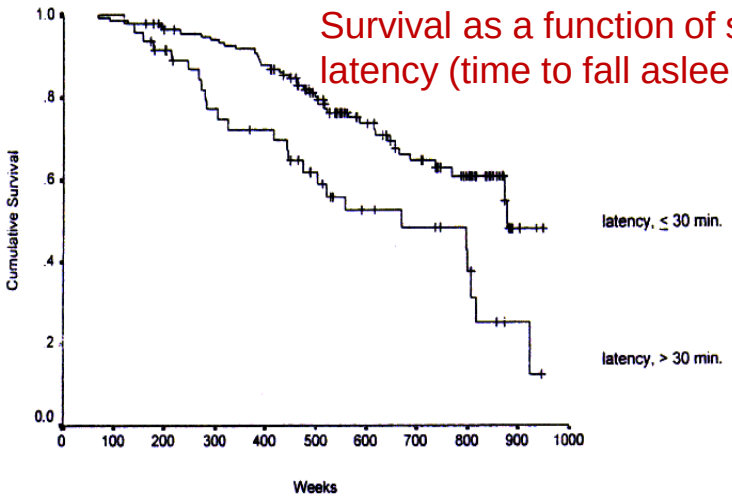
- This talk presents material that is related to one or more of these potential conflicts, and references are provided throughout this lecture as support.

Significance

Insomnia and aging: Significance

- Insomnia is the most prevalent sleep disorder
- Prevalence of insomnia increases with age[1]
- Insomnia is associated with other age-related factors[2,3]
  - Physical, neurological, psychiatric disorders
  - Medications
  - Psychosocial stress
  - Behavioral changes
- Sleep and insomnia affect brain health and overall health
- Treatments of insomnia may affect brain health
  - For better…
  - …or worse





[1]Dodge, *Arch Int Med*, 1995; 155: 1797-1800. [2] Buysse, *JAMA* 2013; 309:706-716. [3]Bloom, JAGS 2009; 57: 761-89. [4]Dew, *Psychosom Med*, 2003; 65:63-73.

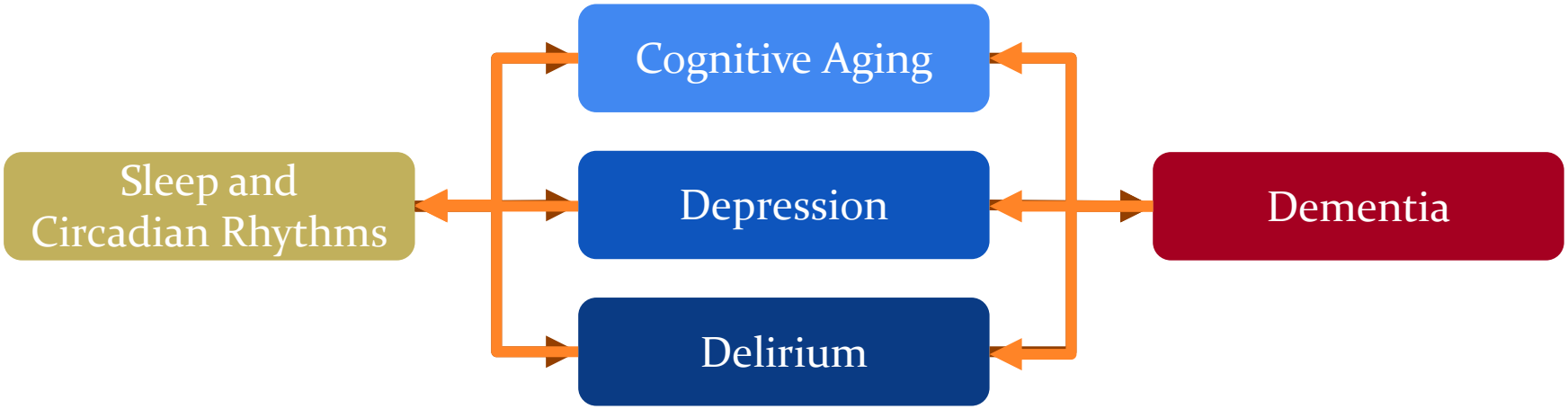
State-of-the-art knowledge

What is insomnia? What is brain health?

- Chronic insomnia disorder[1]
  - Sleep complaint: Difficulty falling asleep, maintaining sleep, or returning to sleep
  - Difficulty in daytime function related to sleep problem
  - Adequate opportunity/circumstances for sleep
- Brain health refers to the ability to remember, learn, plan, concentrate and maintain a clear, active mind.[2]

[1]International Classification of Sleep Disorders, 3rd Edition, American Academy of Sleep Medicine, 2014
[2]brainhealth.gov (DHHS, Administration for Community Living).

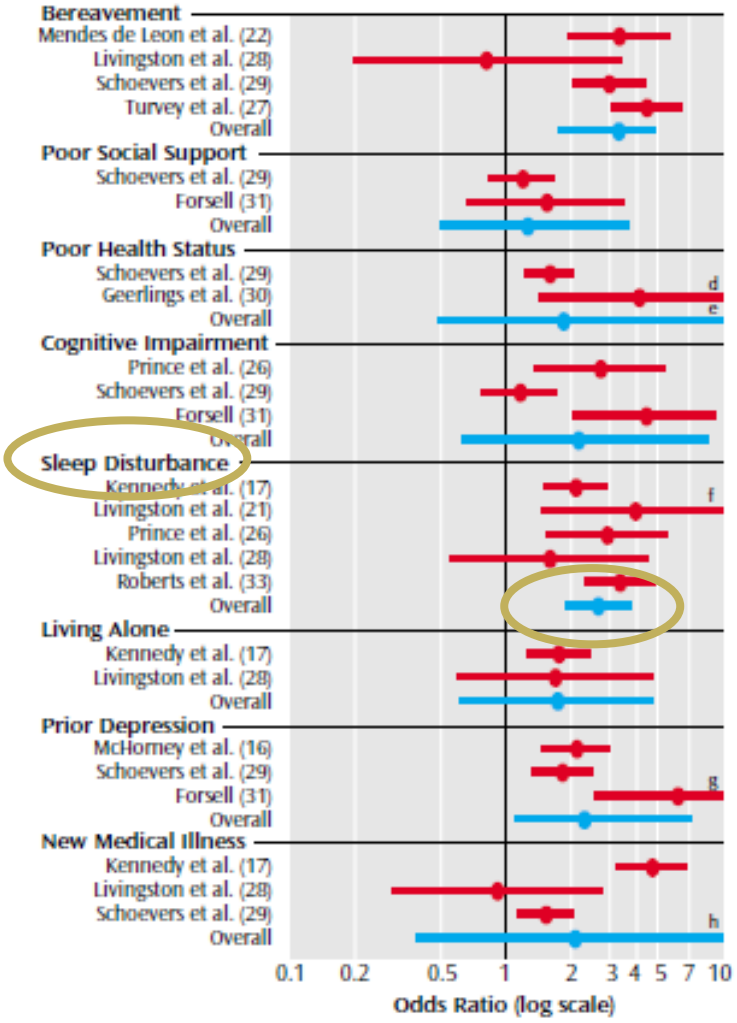
Insomnia and brain health



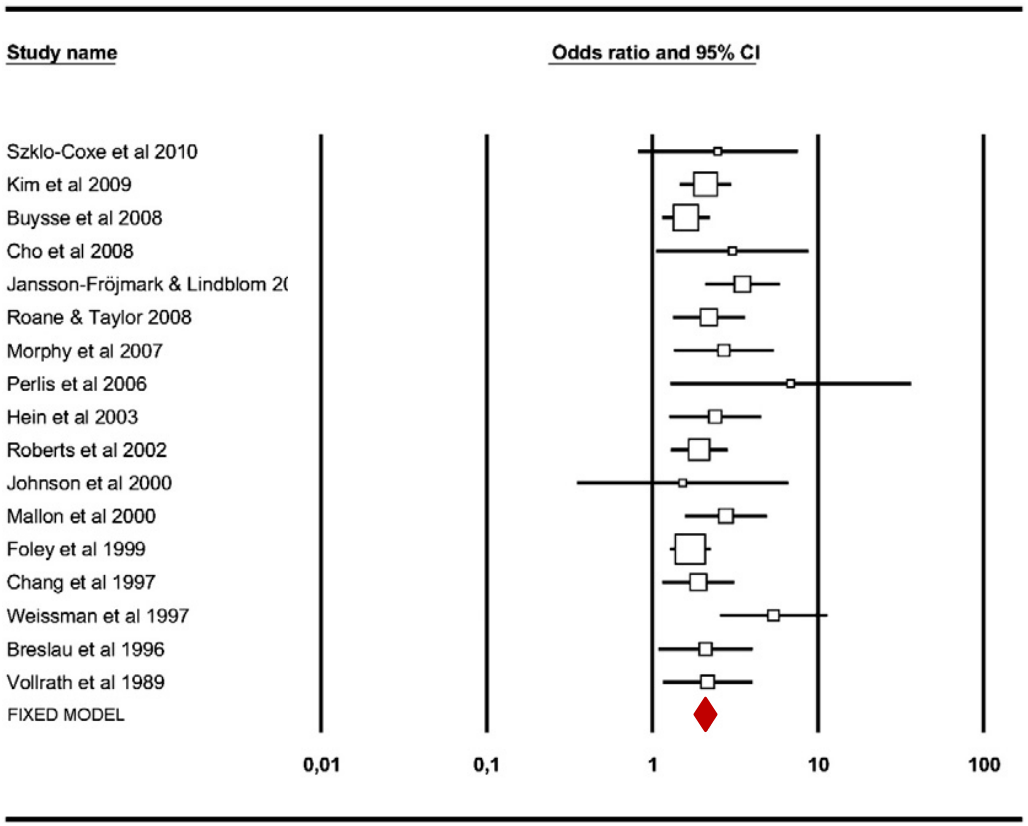
- Key questions
  - How is insomnia related to these indicators of brain health?
  - What are the potential mechanisms?
  - What are the current and emerging treatments, and how might they affect brain health?

Insomnia/sleep disturbance is a risk factor for depression

Sleep disturbance, older adults[1]



Insomnia, all ages[2]

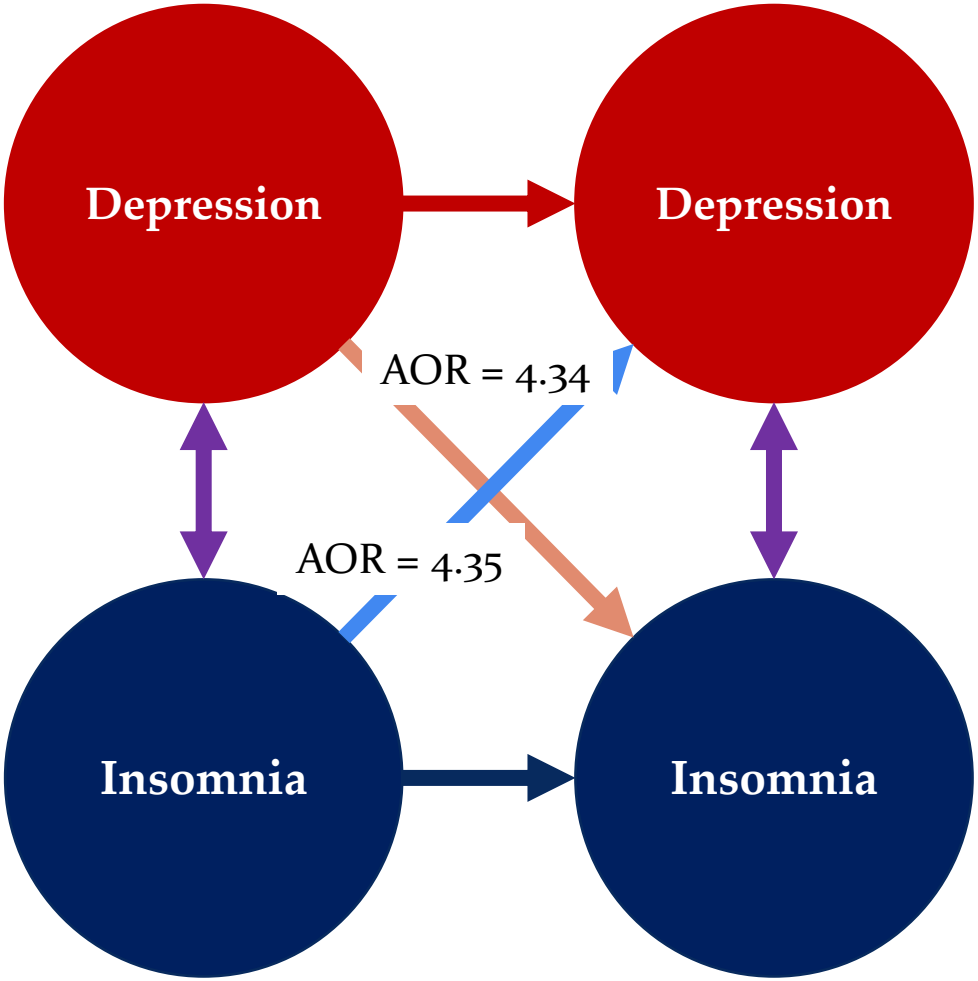


Fixed Model Odds Ratio = 2.10 (1.86 – 2.38)

[1]Cole & Dendukuri, Am J Psychiatry, 2003; 160: 1147-1156
[2]Baglioni, *J Affect Disord* 2011; 135:10-19

Insomnia and depression risk

Bidirectional[1]

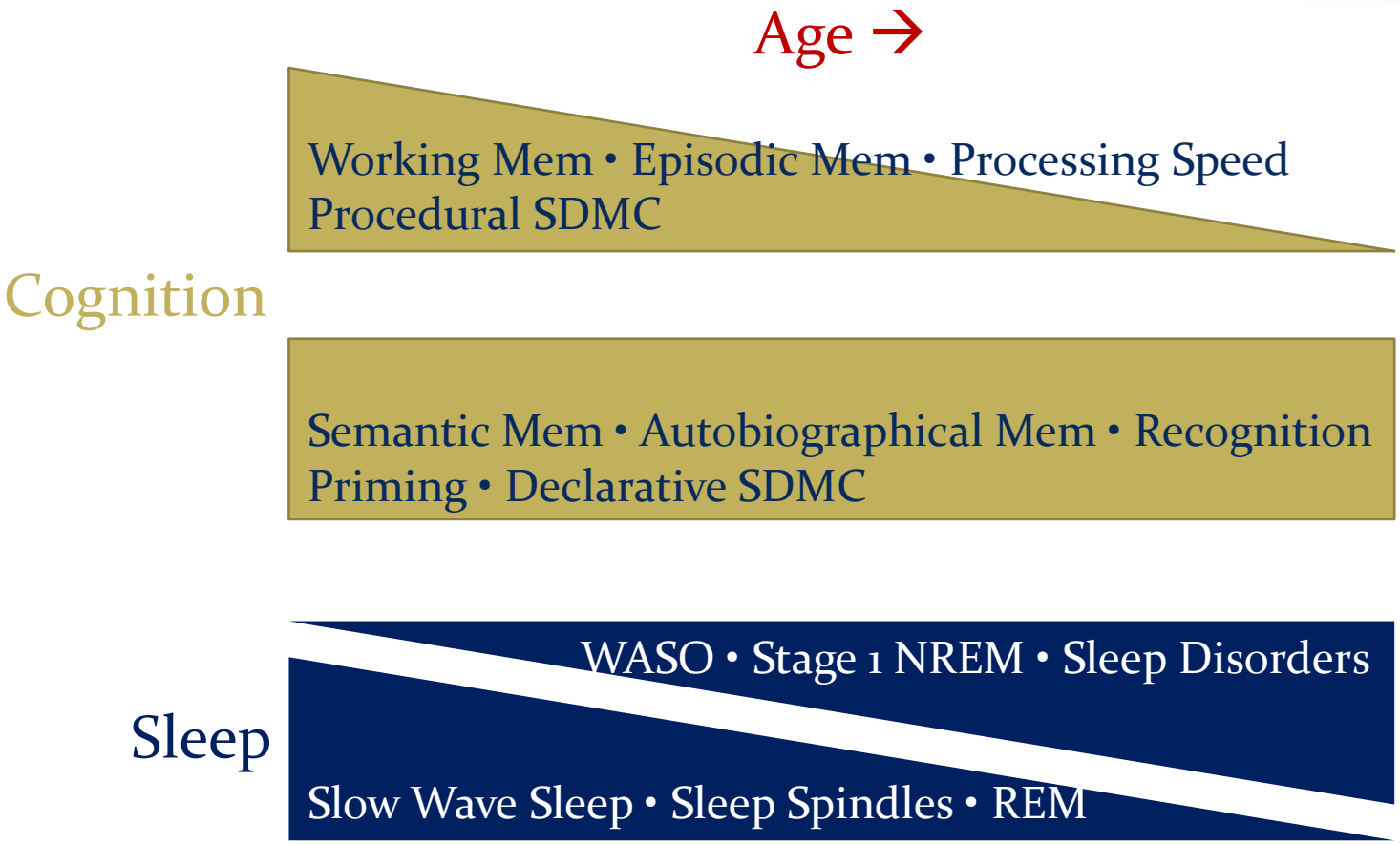


Effects of sleepiness, hypnotics[2]

Symptom (Often)	AOR	p
Poor sleep quality	1.17	<0.0001
Difficulty initiating sleep	1.88	<0.0001
Difficulty maintaining sleep	1.92	<0.0001
Early awakening	1.58	0.0023
Excessive daytime sleepiness	2.15	<0.0001
Prescription hypnotics	1.71	<0.0001

[1]Sivertsen, *Psychosom Med* 2012; 758-765. [2]Jaussent, *SLEEP* 2011; 34: 1103-1110.

Insomnia and cognitive aging



SDMC = Sleep-Dependent Memory Consolidation; WASO = Wake After Sleep Onset; NREM = Non-Rapid Eye Movement; REM = Rapid Eye Movement

Pace-Schott & Spencer, *Curr Topic Behav Nerosci* 2015; 25: 307-330. Scullin & Bliwise, *Persp Psychol Sci* 2015; 10: 97-137

Insomnia and cognitive aging

Aging → Amnestic MCI → Dementia

Cognition

Working Mem • Episodic Mem • Processing Speed
Procedural SDMC

Semantic Mem • Autobiographical Mem • Recognition
Priming • Declarative SDMC

Sleep

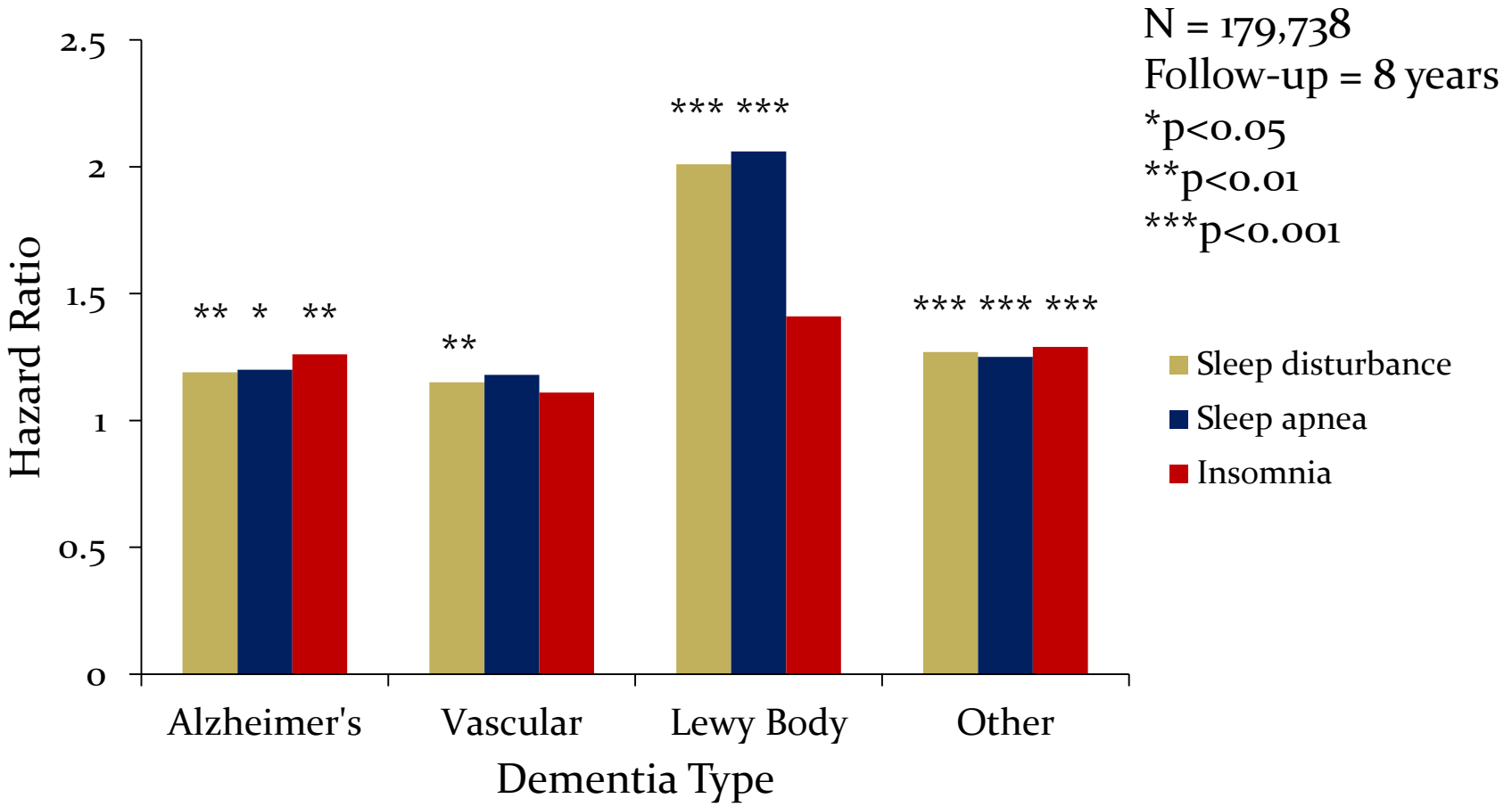
WASO • Stage 1 NREM • Sleep Disorders

Slow Wave Sleep • Sleep Spindles • REM

SDMC = Sleep-Dependent Memory Consolidation; WASO = Wake After Sleep Onset; NREM = Non-Rapid Eye Movement; REM = Rapid Eye Movement

Pace-Schott & Spencer, *Curr Topic Behav Neurosci* 2015; 25: 307-330. Scullin & Bliwise, *Persp Psychol Sci* 2015; 10: 97-137

Sleep disturbances and dementia risk in older veterans



Yaffe, *Am J Geriatr Psychiatry* 2015; 23: 651-654

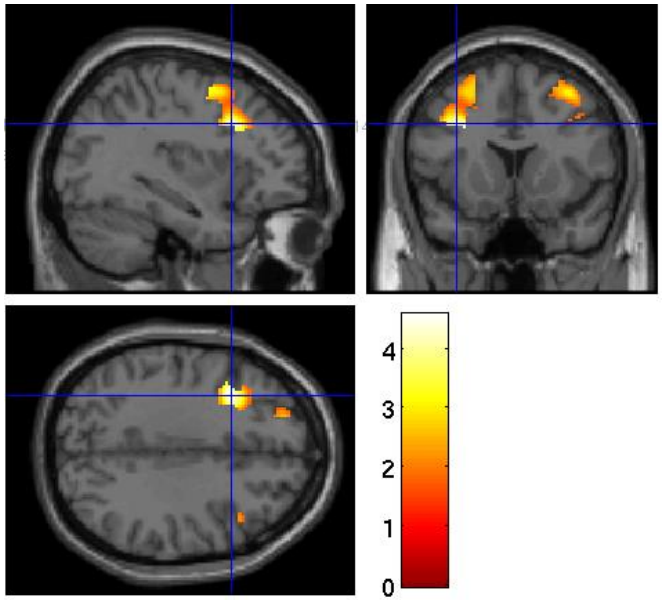
Delirium: Role of sleep-wake and circadian disturbances, melatonin

- Delirium: Acute neuropsychiatric syndrome characterized by disturbances of attention, awareness, consciousness, and cognition, with fluctuating course
- Disturbed sleep and circadian sleep-wake pattern
- Associated with systemic pro-inflammatory cytokines, CNS inflammatory responses
- Reduced plasma melatonin levels in delirium
  - Environmental?
  - Pre-morbid?
- Possible roles of melatonin as therapeutic agent
  - Anti-inflammatory
  - Reduce oxidative stress in CNS
  - *Regulate circadian sleep-wake cycle*

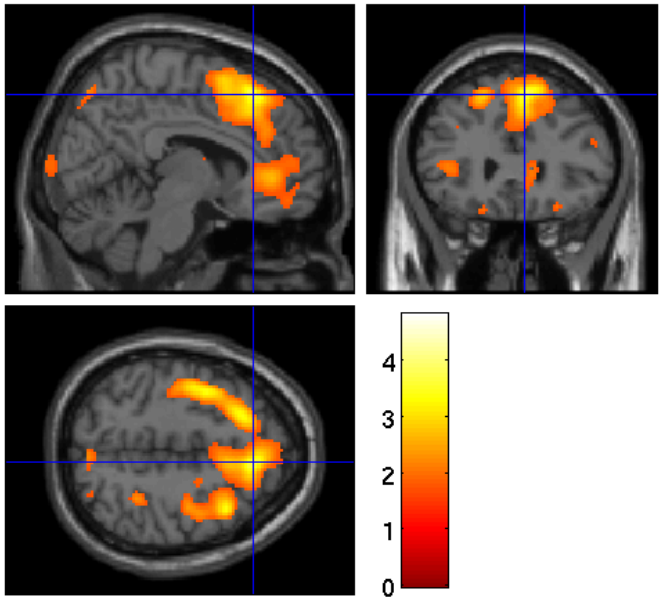
De Rooij and van Munster, *Rejuv Res* 2013; 16: 273-278

NREM slow wave activity is associated with waking prefrontal metabolic rate

Dorsolateral Prefrontal Cortex
(Region of Interest analysis)



Superior Frontal Gyrus
(Whole-brain voxel-wise analysis)



t-maps of positive associations between NREM relative slow wave activity and relative cerebral metabolic rate of glucose during wakefulness. Colors correspond to t-values. Crosshairs indicate peak voxel mapped onto a canonical single subject T1 MR image.

Wilckens, *J Sleep Res*, under review.

Inflammation and autonomic arousal

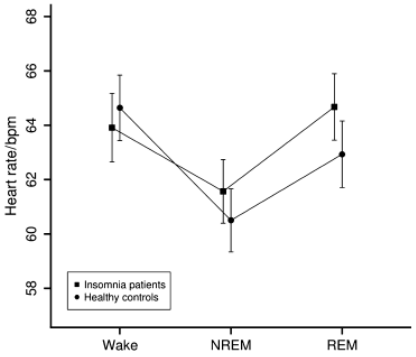
Inflammation[1]

- Sleep disturbance = Poor sleep quality, insomnia symptoms
- Total sample = 41 studies; ~34,000 participants for CRP, ~3000 for IL-6
- Meta-analysis
  - Sleep disturbance and CRP: Effect Size = .12
  - Sleep disturbance and IL-6: Effect Size = .20
- Effects of sleep disturbance on inflammatory markers qualitatively larger than sleep duration (ES = .09-.11)

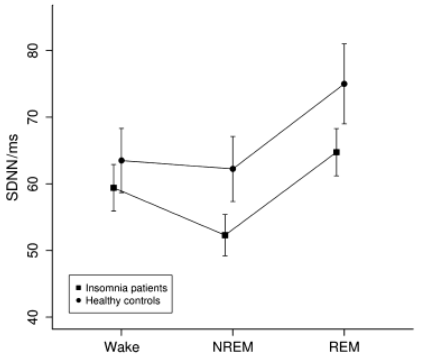
Autonomic arousal

- Most often assessed with hart rate, heart rate variability

Wake-NREM difference smaller in Insomnia (interaction $p < 0.0001$)[2]



Standard deviation smaller in Insomnia ($p = 0.012$)

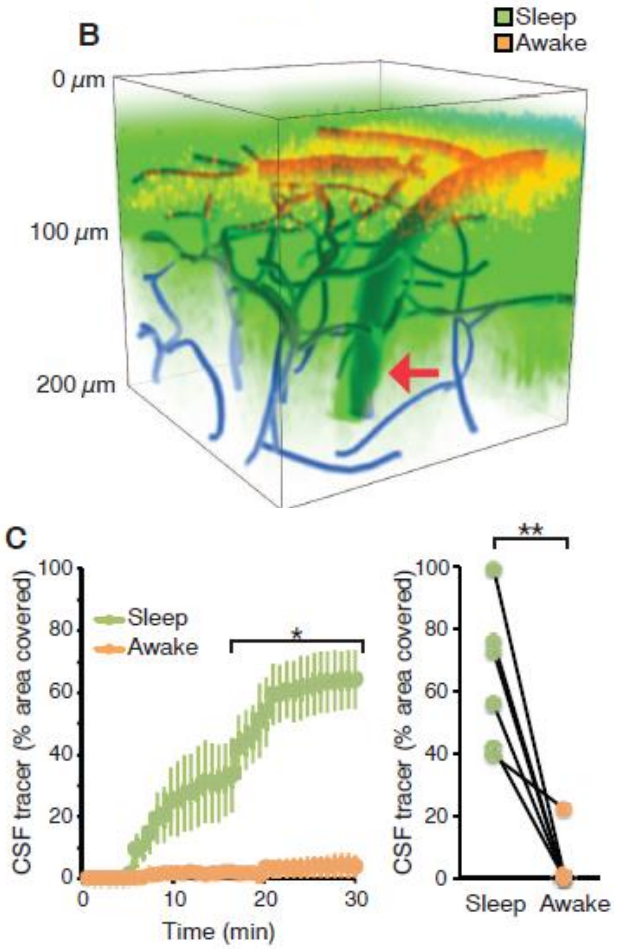


- Insomnia with short sleep duration: Smaller standard deviation, lower high frequency power (parasympathetic)

[1]Irwin, *Biol Psychiatry* 2015; doi: 10.1016/j.biopsych.2015.05.014. [2]Spiegelhalder, *J Sleep Res* 2011; 20: 137-145

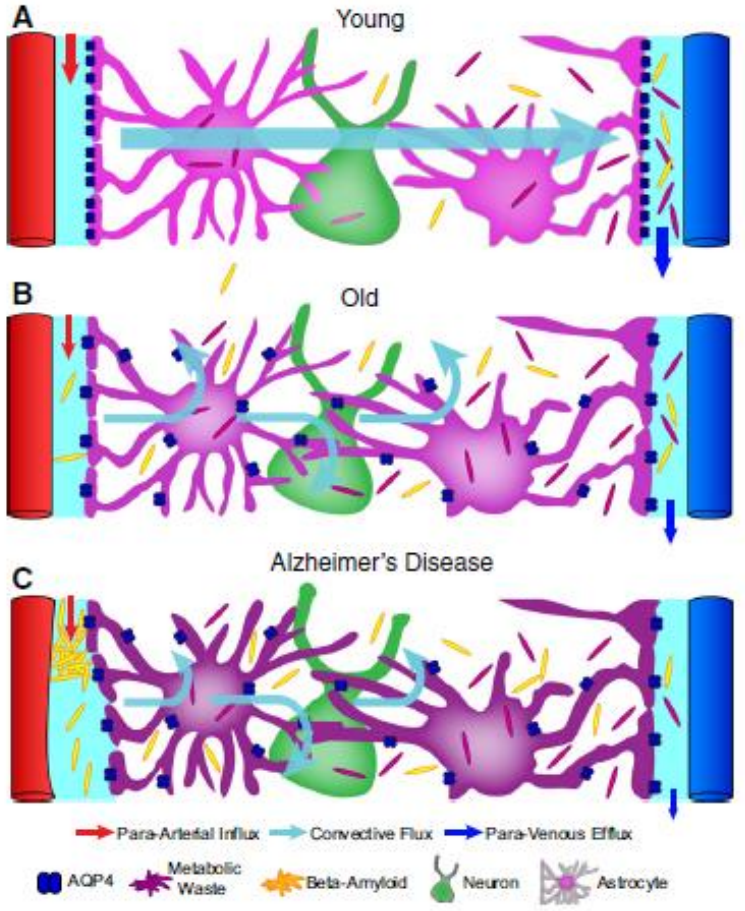
Sleep and the glymphatic system

Increased distribution of CSF tracers during sleep



- Natural sleep and anesthesia result in increased exchange of CSF with interstitial fluid
- Result: Increased β–amyloid clearance during sleep
- Glymphatic system (CSF, interstitial fluid) function mainly during sleep, and are disengaged during wakefulness

Reduced glymphatic function in aging, Alzheimer's disease



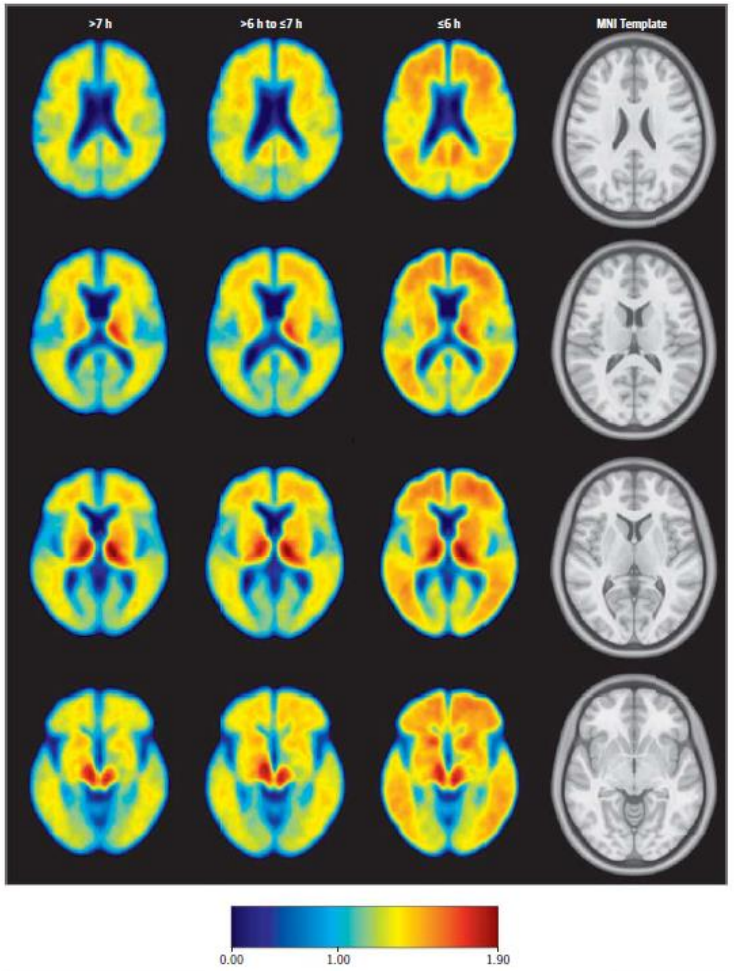
Xie, *Science* 2013; 342: 373-377. Jessen, *Neurochem Res* 2015; DOI 10.1007/s11064-015-1581-6

Sleep duration is associated with β–amyloid in older adults

- n = 70 participants from Baltimore Longitudinal Study of Aging
- Sleep duration by interview
- Amyloid imaging using [^{11}C]PiB PET
- Sleep duration (hours) associated with cortical, precuneus amyloid
- Sleep quality associated with precuneus amyloid
- Trouble falling asleep, awakenings, insomnia rating not associated with amyloid

Hours of Sleep

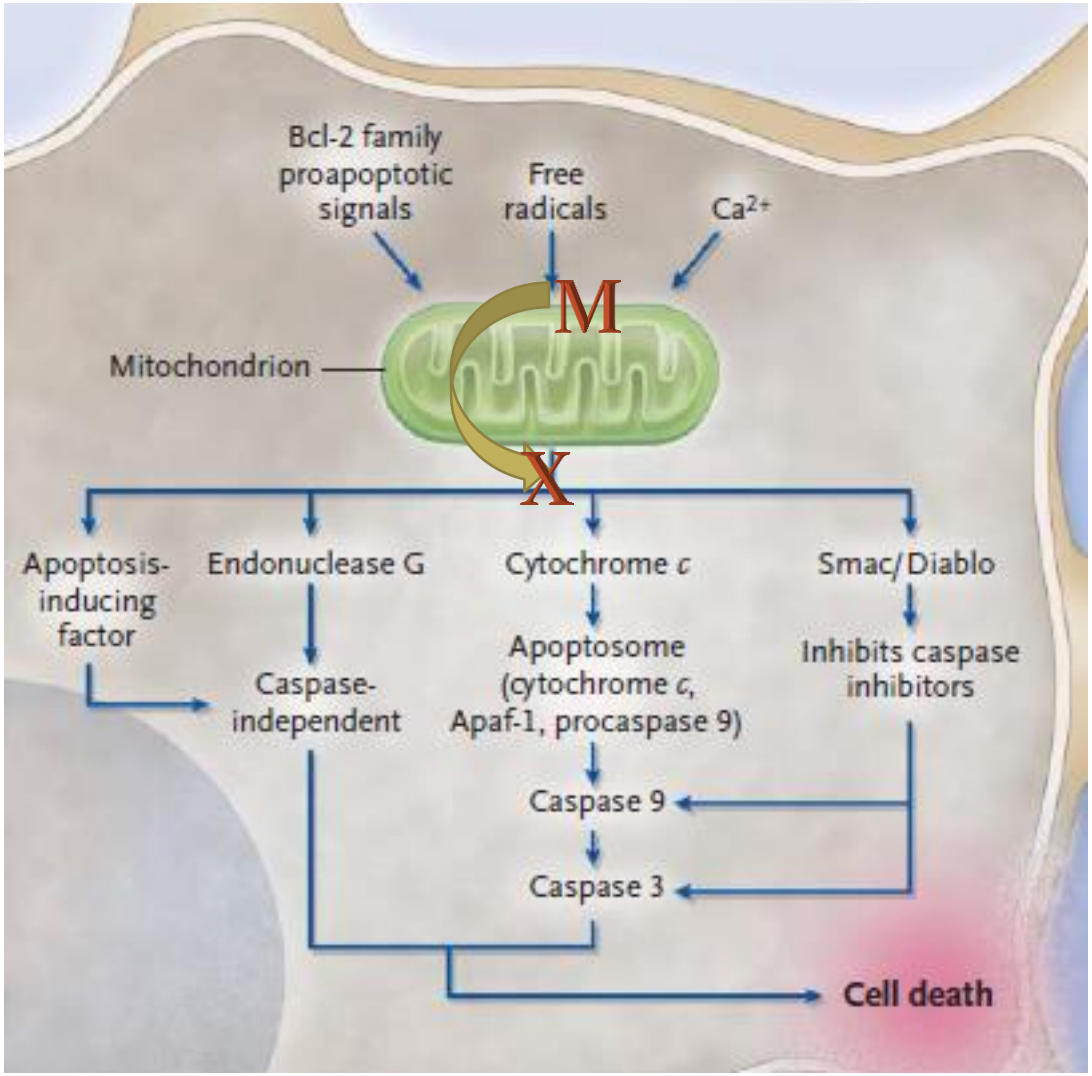
>7 >6 - ≤7 ≤6



Spira, *JAMA Neurol* 2013; 70: 1537-1543

Necrosis, apoptosis, and neuronal cell death: A role for melatonin?

- Mechanism relevant to acute injury (ischemia), neurodegenerative diseases (ALS, Huntington's Disease)
- Melatonin receptors identified on mitochondrial membrane
- Melatonin and precursor *N*-acetylserotonin (NAS) provide neuroprotection from ischemia by inhibiting mitochondrial apoptogenic factors
- ***Relevance of age-related reduction in melatonin secretion?***



Friedlander, *NEJM* 2003; 348: 1365-1375. Zhou, *J Neurosci* 2014; 34:2967-2978.

Medications used to treat insomnia

Medication Class	Examples	Potential Advantages	Potential Disadvantages
Benzodiazepine receptor agonists (BzRA)	Zolpidem, zaleplon, eszopiclone, temazepam	• Efficacious • Variety of half-lives	• Cognitive effects • Falls • Dependence
Sedating antidepressants	Doxepin, amitriptyline, nortriptyline	• No abuse • Effective for WASO	• Anticholinergic • Cardiac effects • Falls
Antihistamines	Diphenhydramine, doxylamine	• Widely available	• Cognitive effects • Limited efficacy data
Melatonin, receptor agonist	Melatonin, ramelteon	• "Natural" mechanism • Some efficacy data	• Limited efficacy on WASO
Orexin antgonist	Suvorexant	• Novel mechanism, blocks wake signal	• Limited efficacy, effectiveness data
Sedating antipsychotics	Quetiapine, olanzapine	• Not BzRA • Efficacy for psychosis, depression	• Metabolic, neurological, cardiovascular effects
Miscellaneous	Gabapentin, pregabalin	• Not BzRA • Efficacy for pain	• Limited sleep efficacy data

WASO = Wakefulness After Sleep Onset. *Italics = Not FDA-approved for insomnia*

Medications used to treat insomnia

Medication Class	Examples	Potential Advantages	Potential Disadvantages
Benzodiazepine receptor agonists (BzRA)	Zolpidem, zaleplon, eszopiclone, temazepam	• Efficacious • Variety of half-lives	• Cognitive effects • Falls • Dependence
Sedati… antide…			
Antihi…			…a
Melato… recept…			
Orexin… antagonist	…suvorexant	blocks wake signal	effectiveness data
Sedating antipsychotics	Quetiapine, olanzapine	• Not BzRA • Efficacy for psychosis, depression	• Metabolic, neurological, cardiovascular effects
Miscellaneous	Gabapentin, pregabalin	• Not BzRA • Efficacy for pain	• Limited sleep efficacy data

The ugly truth about drugs for insomnia in older adults

- Benzodiazepine receptor agonists have significant side effects and safety concerns
- Other alternatives have not been systematically evaluated for efficacy or safety
- Is ANY sedating drug "safe" in older adults?

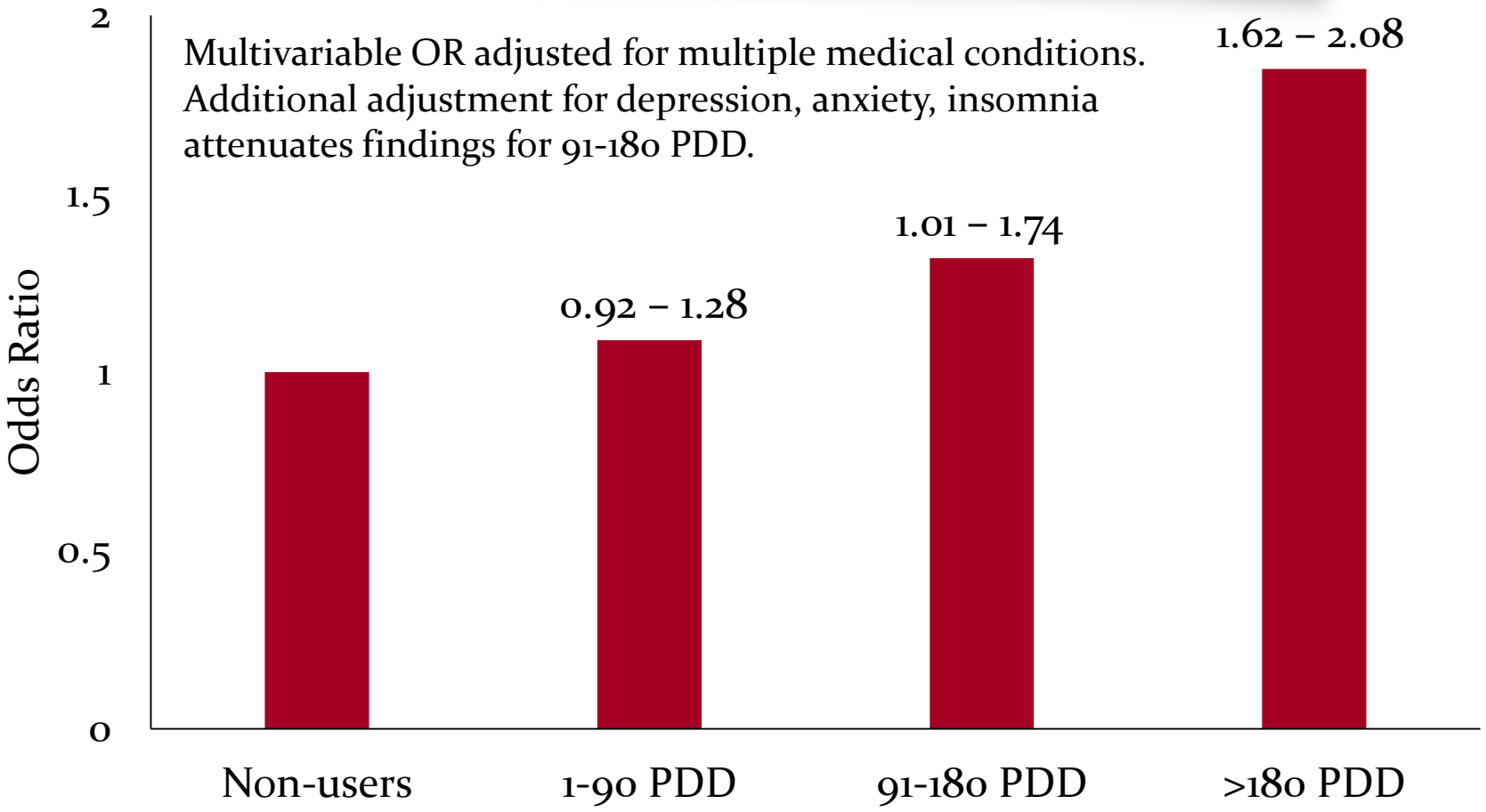
WASO = Wakefulness After Sleep Onset. *Italics = Not FDA-approved for insomnia*

Meta-analyses of benzodiazepine receptor agonist effects in insomnia[1]

- Statistically significant effect for self-report and/or PSG outcomes (sleep quality, sleep latency, WASO, TST)
- Most studies short-term
- Older adults[2]
  - Reduced efficacy
    - Sleep quality effect size: 0.14
    - Number Needed to Treat: 13
  - Side effects significant
    - Adverse effects odds ratios: 2.25-4.78
    - Number Needed to Harm: 6

[1]Buysse, *JAMA* 2013; 309:706-716. [2]Glass, *BMJ* 2005;331: 1169-1175. Nowell, *JAMA* 1997;278(24):2170-2177. Holbrook, *CMAJ* 2000;162(2):225-233. Smith, *Am J Psychiatry* 2002;159(1):5-11. Dundar, *Health Technol Assess* 2004;8(24): 111-125. Buscemi, *J Gen Intern Med* 2007;22(9):1335-1350.

Benzodiazepine use and risk of Alzheimer's disease: Case-control study



OR for short-acting Bz 1.43 (1.27-1.61)
OR for long-acting Bz 1.70 (1.46-1.98)
PDD = Prescribed daily doses

Billioti de Gage, *BMJ* 2014; 349.

Cognitive and behavioral treatments for insomnia

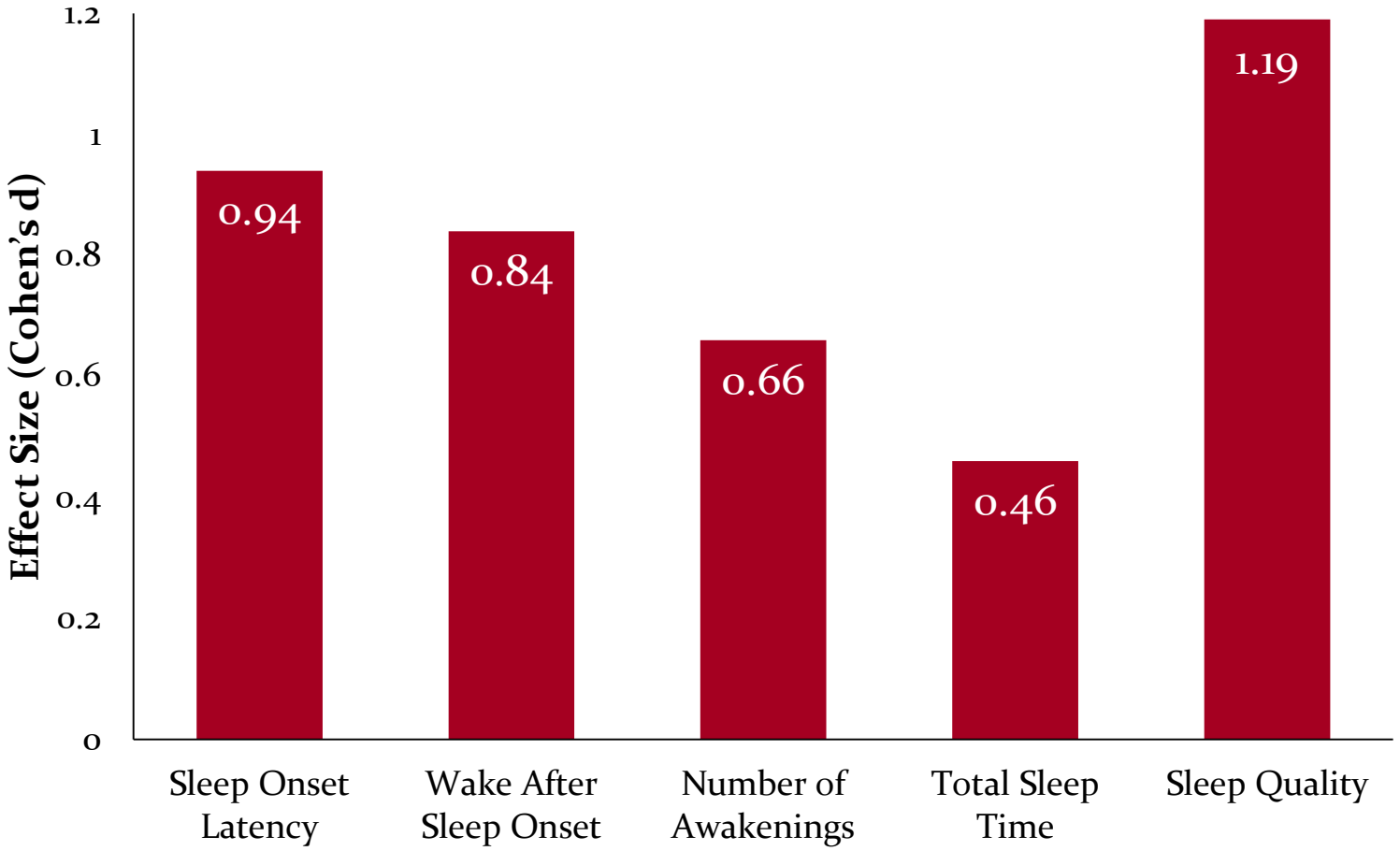
Technique	Aim
"Sleep hygiene" education	Promote habits that help sleep; eliminate habits that hurt sleep
Stimulus control	Strengthen bed/bedroom as sleep stimulus
Sleep restriction therapy	Restrict time in bed to improve sleep depth/consolidation
Cognitive therapy	Address maladaptive thoughts and beliefs; behavioral experiments
Relaxation training	Reduce physical/psychological arousal
Cognitive Behavioral Therapy for Insomnia (CBTI)	Combines elements of each of the above techniques

Cognitive and behavioral treatments for insomnia

Technique	Aim
"Sleep hygiene" education	Promote habits that help sleep; eliminate habits that hurt sleep
Stimulus control	Strengthen bed/bedroom as sleep stimulus
Sleep re	
Cogniti	fs;
Relaxation training	Reduce physical/psychological arousal
Cognitive Behavioral Therapy for Insomnia (CBTI)	Combines elements of each of the above techniques

A diverse set of behavioral prescriptions designed to improve the quality of nocturnal sleep

Efficacy of Cognitive Behavioral Therapy for Insomnia (CBT-I)



Morin, 2010, in Kryger, Roth & Dement (Eds.), *Principles and Practices of Sleep Medicine*

Cognitive-behavioral treatments for insomnia: New approaches

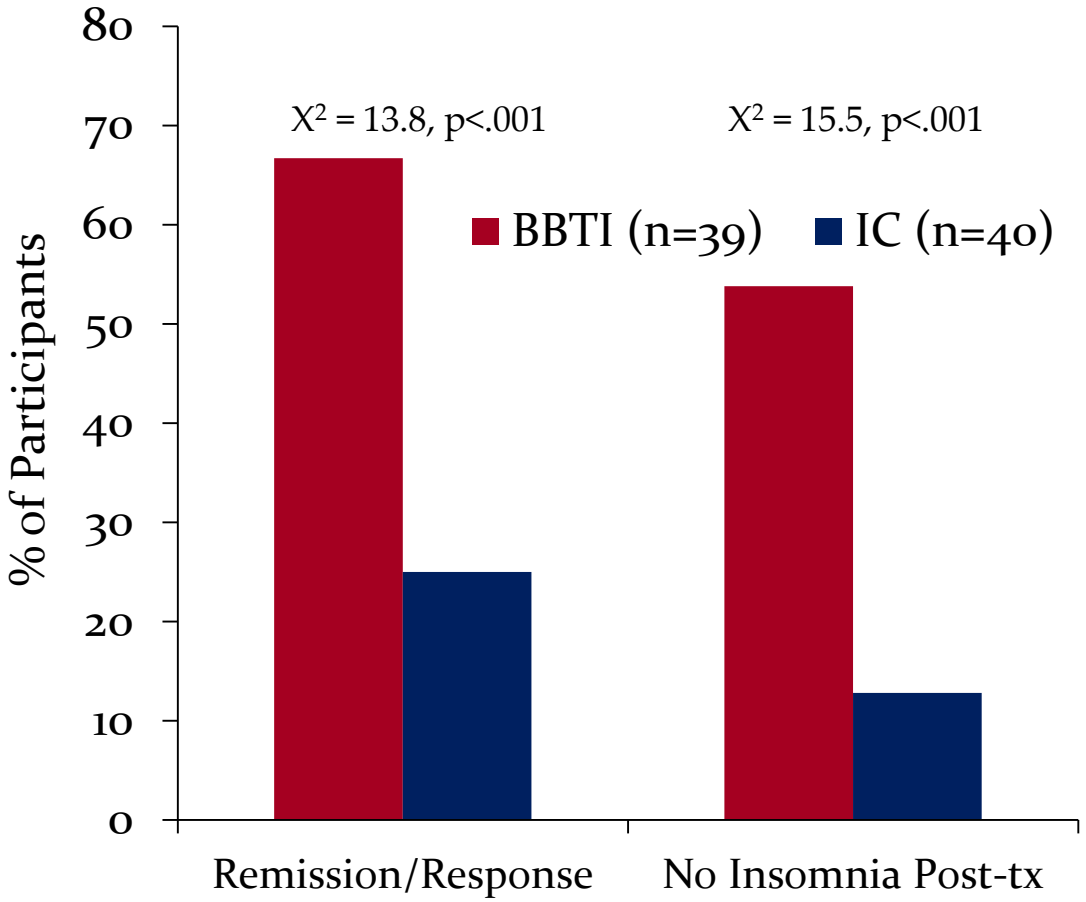
- Brief(er) Treatments
  - Brief Behavioral Treatment for Insomnia[1,8]
  - ≤4 sessions, single session treatments, classroom/lecture
- Single-component treatments (stimulus control, sleep restriction)[9]
- Other types of therapists
  - Master's-level therapist,[2] nurse, social worker, peer specialist
- Groups[3,8]
- Telephone[4], Video tele-health/Skype™ [5]
- Self-help approaches[6]
- Online treatments: Sleepio™, Shuti™, others[7]
- Mobile app-based: VA CBTI coach, iREST™, multi-user health kiosks

[1]Buysse, 2011; *Arch Int Med* 171(10):887-895. [2]Fields, 2013; *J Clin Sleep Med* 9(10):1093-1096. [3]Koffel, 2015; *Sleep Med Rev* 19:6-16. [4]Arnedt, 2013; *SLEEP* 36(3):353-362. [5]Savard, 2014; *SLEEP* 37(8):1305-1314. [6]Ho, 2015; *Sleep Med Rev* 19:17-28. [7]Cheng, 2012; *Psychother Psychosom* 81(4):206-216. [8]Lovato, 2014; *SLEEP* 37:117-126. [9]Epstein, 2012; *SLEEP* 35:795-805.

Acute response to BBTI vs. information control (IC) in older adults with chronic insomnia

Brief Behavioral Treatment of Insomnia (BBTI)

- Reduce your time in bed
- Get up at the same time every day of the week, no matter how much you slept the night before
- Don't go to bed unless you're sleepy
- Don't stay in bed unless you're asleep



Buysse, *Arch Int Med*, 2011; 171:887-895

Treatment of insomnia improves other symptoms related to brain health

- Comorbid depression
  - Greater reduction of insomnia and depression symptoms with CBT-I vs. control[1]
  - CBT-I shows larger effect on insomnia symptoms, equal effect on depression symptoms compared to CBT for depression[2]
- Pain[3]
  - N = 367 older adults with insomnia + osteoarthritis
  - Randomly assigned to CBT for pain, CBT for pain + insomnia, Education Control
  - At 9 and 18 month follow-up, insomnia improvement associated with
    - Better sleep
    - Less fatigue
    - Lower pain severity, arthritis symptoms

[1]Manber, *SLEEP* 2008; [2]Blom, *SLEEP*, 2015; 38: 267-277. [3]Vitiello, *PAIN*, 2014; 155: 1547-1554

Insomnia, insomnia treatment, and cognitive function

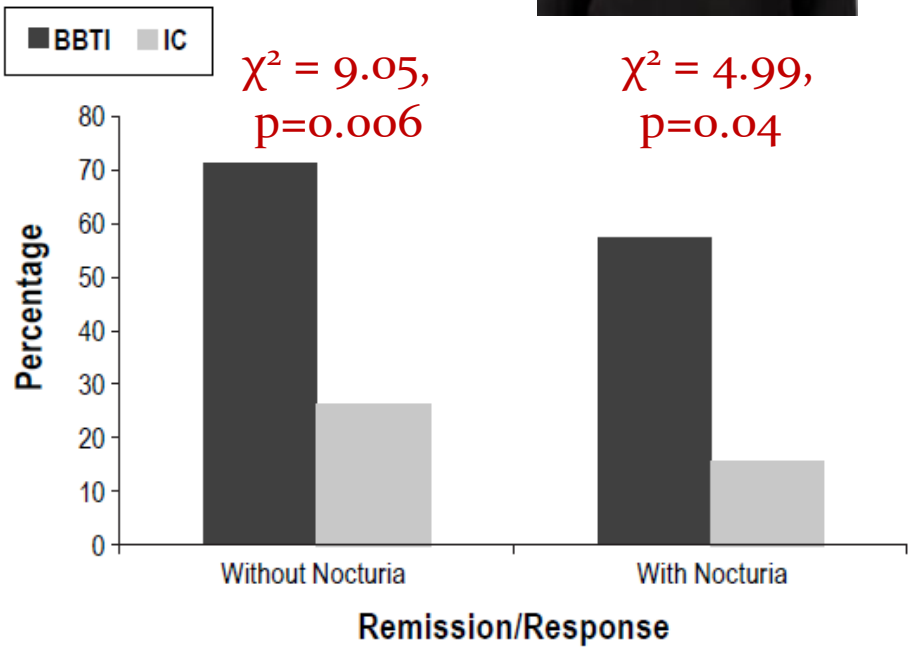
- Older adults with insomnia (n = 77)
- Tests of episodic memory, working memory, abstract reasoning
- Baseline
  - WASO associated with delayed recall
  - NREM delta, sigma power associated with abstract reasoning, working memory
- Post-Intervention with BBTI or information control
  - No overall effect of treatment type
  - Increase in delta associated with improved abstract reasoning

BBTI = Brief Behavioral Treatment of Insomnia. WASO = Wake After Sleep Onset. Wilckens, *Behav Sleep Med*, 2015; DOI: 10.10801/15402002.2014.1002034

Insomnia, insomnia treatment, and nocturia

- Improvement in nocturia with BBTI[1]
  - 30 older adults with insomnia and nocturia
  - Randomly assigned to BBTI (n=14) or control (n=16)
  - BBTI associated with significant reduction in nocturia compared to control (p=.04, *d*=0.82)

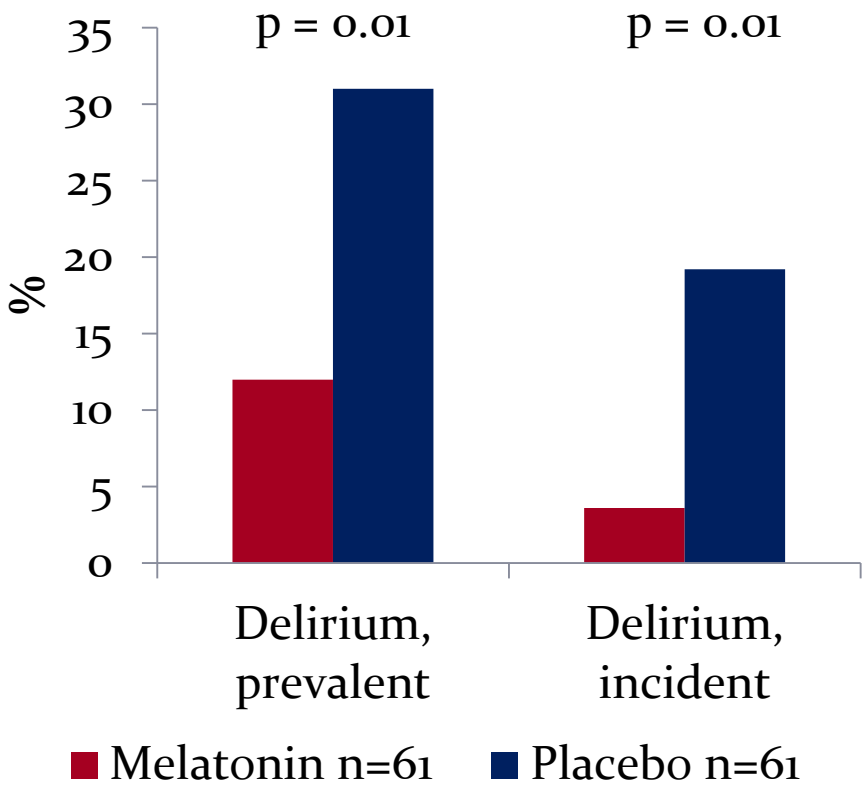
- Smaller magnitude of BBTI response among insomnia patients with nocturia[2]
  - True for sleep diary, actigraphy, and categorical outcomes
  - No differences by nocturia in polysomnography



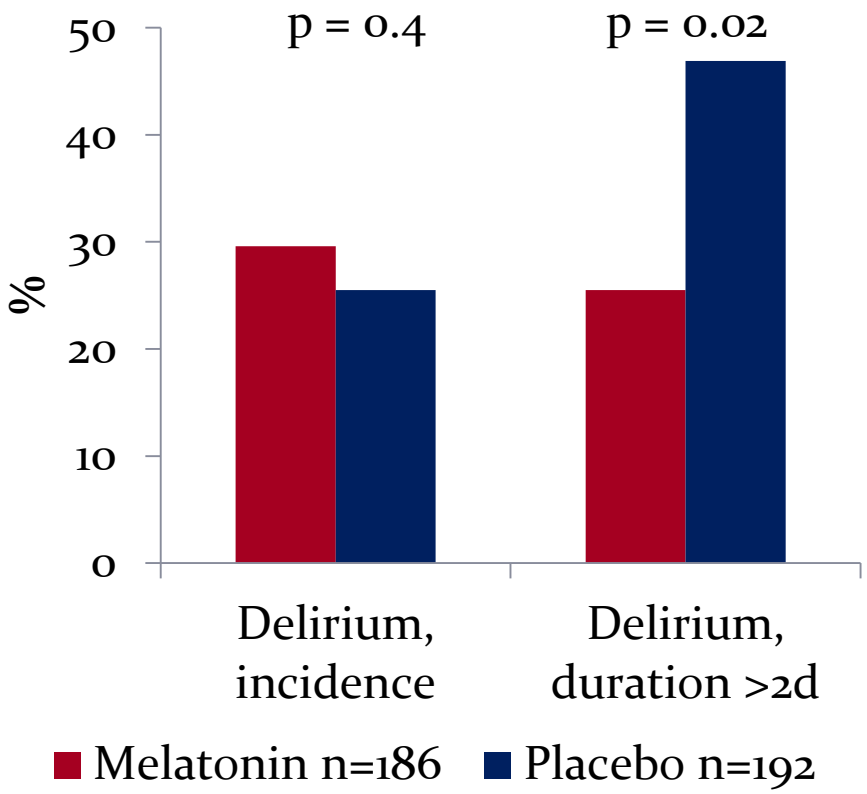
BBTI = Brief Behavioral Treatment of Insomnia. [1]Tyagi, *JAGS*, 2014; 62: 54-60. [2]Tyagi, *SLEEP*, 2014; 37:681-687.

Melatonin treatment of delirium

Emergency medical admissions, >65 y.o.[1]
Melatonin 0.5 mg



Acute hip fracture, >65 y.o.[2]
Melatonin 3 mg



[1]Al-Aama, *Int J Geriatr Psychiatry*, 2011; 26: 687-694. [2]de Jonghe, *CMAJ*, 2014; 186: E547-E556.

CBT-I affects mechanisms, correlates of insomnia

- "Normalized" regional metabolism in precuneus, posterior cingulate during wake and NREM sleep
- Reduced proportion of patients with elevated C-Reactive Protein[1]
- Reduced proportion of patients with elevated multi-system biological risk profile (high-density lipoprotein, low-density lipoprotein, triglycerides, hemoglobin A1c, glucose, insulin, C-reactive protein, fibrinogen)[2]

[1]Irwin, *SLEEP*, 2014; 37: 1543-1552. Carroll, *Psychoneuroendocrinol*, 2015; 55: 184-19

Knowledge gaps

Knowledge gaps

- Direction of insomnia-brain health relationships
  - Unidirectional? Which direction? Bidirectional?
- Which sleep measure(s)?
  - Insomnia
  - Continuous sleep measures
  - Self-report, behavioral, polysomnographic
  - Multiple dimensions of sleep health
- Mechanisms underlying insomnia-brain health relationships
  - How does sleep confer neural plasticity in aging?
  - How does sleep lead to systemic effects?
- Interventions
  - Can sleep interventions ameliorate changes in brain health?
  - What are the limits? Can insomnia effects always be reversed?
  - When are interventions most timely?
  - Do interventions target the right mechanisms?

Research opportunities

Research opportunities

- Incorporate broad and deep sleep/ circadian measures in longitudinal brain health cohorts
  - Self-report, behavioral, physiological, polysomnographic, imaging, genetic measures
  - Multi-dimensional measures
  - Which aspects of sleep are most important for brain health?
- Investigate mechanisms by which sleep and circadian rhythms affect brain health
  - Neuroimaging during sleep, wakefulness
  - Inflammation, autonomic tone
  - Genetic, gene expression studies in relation to sleep, circadian rhythms

Research opportunities

- Intervention studies
  - *Prevention* as well as treatment?
  - Novel behavioral interventions
    - Might sleep restriction counteract benefits for cognition?
  - Novel drugs based on mechanism of sleep/circadian effects
  - Mechanisms of behavioral and pharmacologic treatment effects
  - Long-term trajectory of treatment effects on brain health
    - e.g., effects of sleep interventions on cognitive impairment, dementia
  - Sleep and circadian interventions: Sleep health
    - Tie together sleep, physical activity, nutrition

Expanded framework for investigating sleep, health, and sleep health in aging