

UCSD Department of Medicine Grand Rounds
March 15, 2023

Sleep in Older Adults: Why Can't Grandma Sleep?

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1

Disclosures

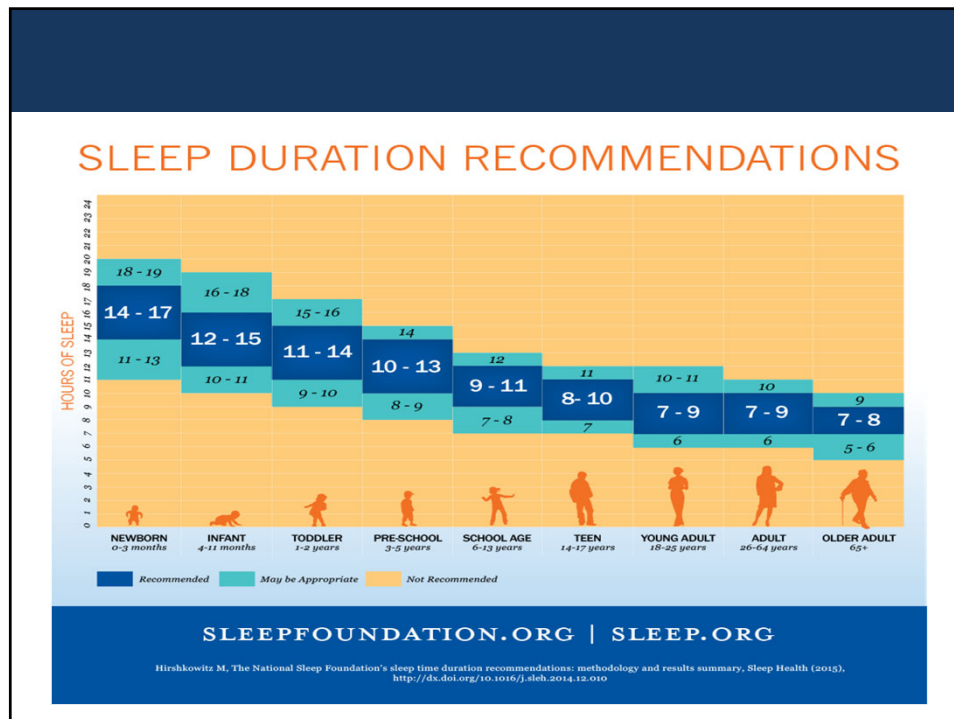
- Consultant/Scientific Advisory Board:
 - Eisai, Biogen, Idorsia, Merck, PureTech, Wesper
- Royalties:
 - Medscape; Up-To-Date

2

Learning Objectives

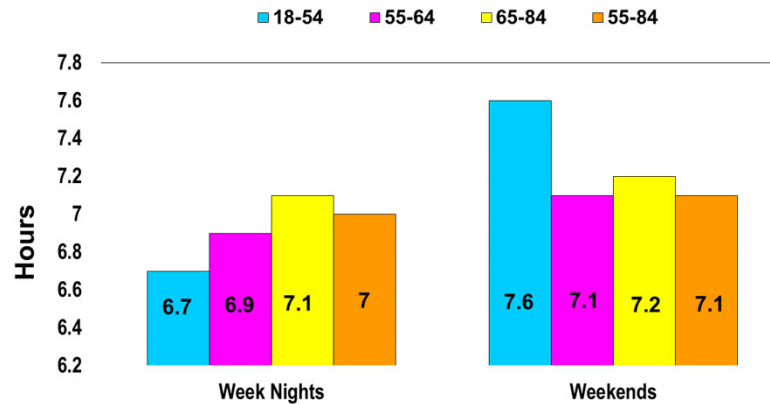
- ▶ After this session, you will be able to:
 1. Identify changes in sleep architecture with age
 2. Understand consequences of poor sleep in older adults
 3. Identify co-morbidities often associated with poor sleep in older adults
 4. Identify primary sleep disorders common in older adults and their treatment
 5. Learn about the association between OSA and cognition/dementia

3



4

Reported Hours Slept Older vs. Younger American Adults



2003 NSF Sleep in America Poll

5

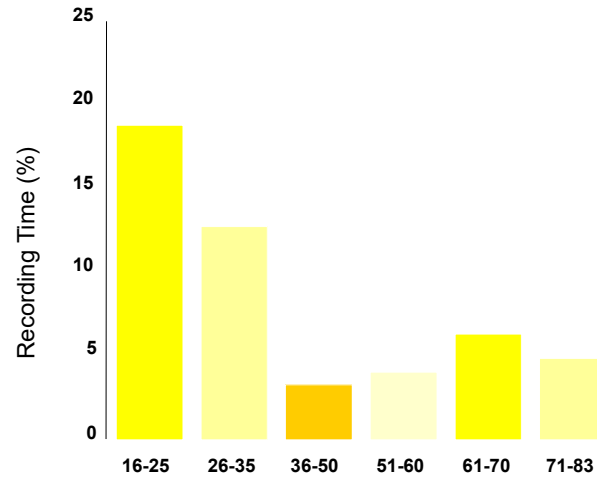
Changes in Sleep with Age

- Meta-analytic review of 65 sleep studies in healthy persons
 - 3557 total subjects aged 5-102 years
- Most age-related sleep changes occur in early and mid-years of human life span
- In healthy older adults:
 - Sleep remains relatively constant from age 60 to mid-90s
 - Except for SE which decreases

Ohayon MM et al. *Sleep*. 2004, 27:1255-1273.

6

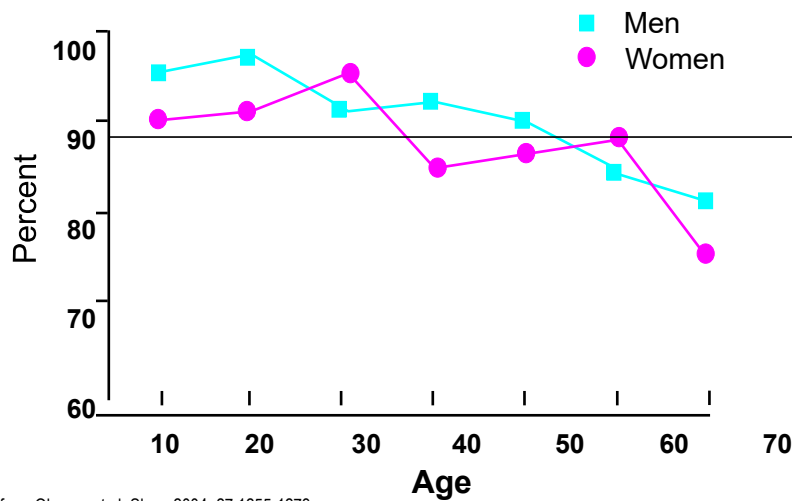
Slow Wave Sleep



Van Cauter E et al. *JAMA*. 2000;284:861-868.

7

Changes with Age: Sleep Efficiency



Modified from Ohayon et al. *Sleep* 2004, 27:1255-1273

8

Why does sleep deteriorate as we get older?

- Is it aging?
 - NO
- Age per se does NOT cause sleep problems
- BUT, all the things that go along with aging, do

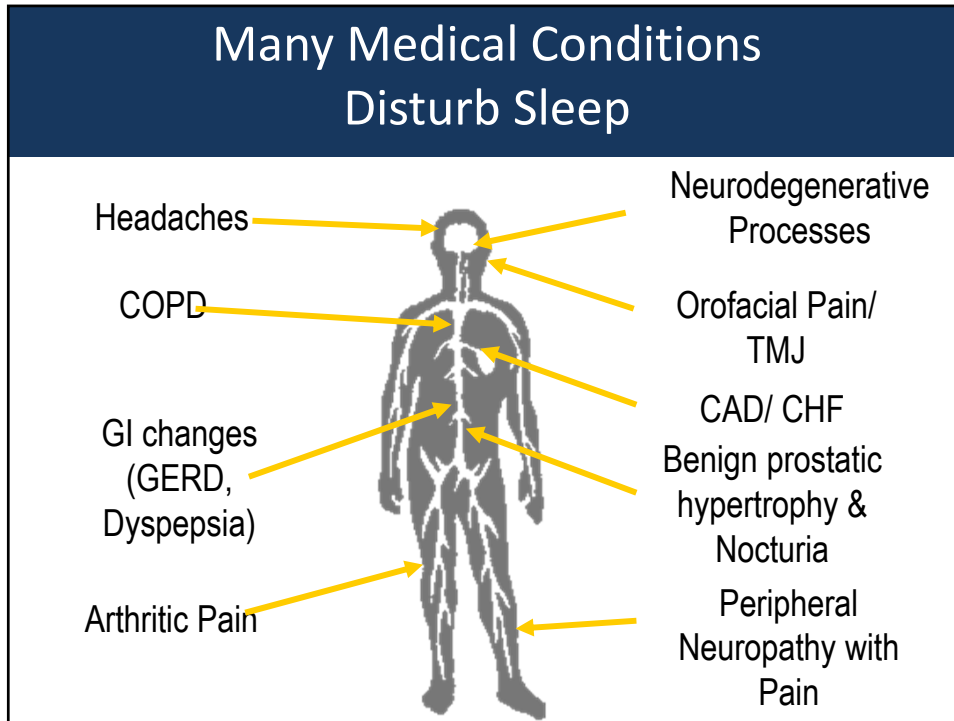
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Factors Affecting Ability to Sleep in the Elderly

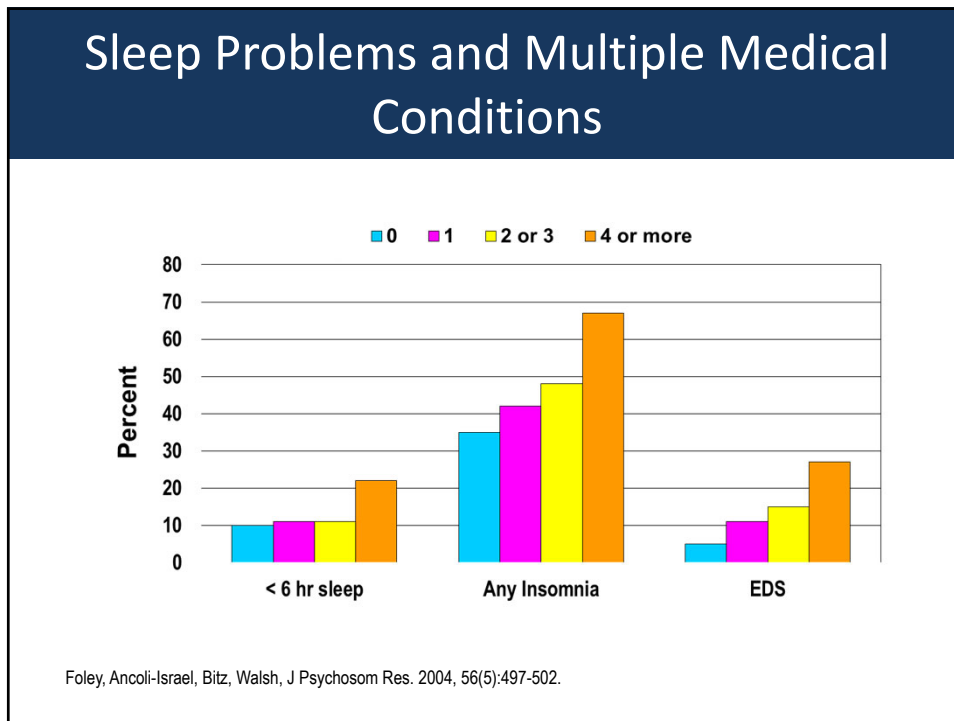
- Medical/psychiatric illness
- Medications/polypharmacy
- Circadian rhythm disturbances
- Primary sleep disorders
 - Insomnia
 - Sleep apnea
 - REM Behavior Disorder
 - Restless Legs Syndrome/Periodic Limb Movements in Sleep

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000:597-661.

10



11



12

Sleep disturbance and depression in older men (MrOS sleep study; n=3051)

Depressive symptoms have a strong, graded association with subjective sleep disturbances and are moderately associated with objectively measured prolonged sleep latency

	Normal (n=2310)	Depressive symptoms (n=537)	Depression (n=204)	P-value
<u>Subjective (PSQI)</u>				
Pittsburgh Sleep Quality Index >5	1.0 (referent)	2.06 (95% CI 1.67-2.55)	3.68 (95% CI 2.54-5.33)	<0.001
<u>Objective (5-days actigraphy)</u>				
Sleep latency \geq 1 hour	1.0 (referent)	1.40 (1.03-1.90)	1.68 (1.08-2.61)	0.006

All analyses adjusted for age, clinic site, race, body mass index, living alone, alcohol intake, smoking status, cognitive impairment, physical activity, certain medical conditions, education, self-reported health status, IADL impairments, and use of antidepressants, benzodiazepines and non-benzodiazepine anxiolytic/hypnotics.

Paudel et al, J Am Geriatr Soc. 2008 Jul;56(7):1228-35

13

Consequences of Disturbed Sleep

- Difficulty sustaining attention
- Slowed response time
- Difficulty with memory
- Decreased performance
- Higher risk of
 - depression
 - poor physical function
 - cognitive impairment
 - falls
 - mortality

May all be misinterpreted as dementia

Ancoli-Israel S, Roth T. *Sleep*. 1999;22(suppl 2):S347-S353; Ancoli-Israel, 2000, *Sleep*, 23 (suppl), S23 - S30; Blackwell, Yaffe, Ancoli-Israel et al, *J Gerontol: MED SCI*, 2006, 61A(4):405-410; Dam, Ewing, Ancoli-Israel et al, *JAGS*, 2008 56(9):1665-73; Paudel et al, *J Am Geriatr Soc*. 2008 Jul;56(7):1228-35; Stone,K.L., Ewing,S.K., Lui,L.Y., Ensrud,K.E., Ancoli-Israel,S., et al. *JAGS* 54:1177-1183, 2006; Stone,K.L., Ancoli-Israel,S., Blackwell,T., et al. *Arch. Intern. Med.* :168(16):1768-1775:2008

14

Sleep disturbance and physical function in older men (MrOS sleep study; n= 2,862, >67y/o)

- Lighter and more fragmented sleep were associated with poorer performance
 - In age adjusted models, shorter TST, SE<80%, WASO \geq 90 min, were associated with lower grip strength, slower walking speed, inability to stand from a chair without assistance, and inability to complete a narrow walk course

	Inability to Perform Chair Stand	Inability to Perform Narrow Walk	P-value
SE<80%	1.72 (95% CI 1.19, 2.49)	1.34 (95% CI 1.08, 1.66)	<0.05
WASO>90 min	1.73 (95% CI 1.20, 2.49)	1.33 (95% CI 1.07, 1.64)	<0.05

All analyses adjusted for age, BMI, clinic site, antidepressant use, hypertension, comorbid disease (history of at least one medical condition including cardiovascular disease, osteoarthritis, diabetes, COPD and Parkinson's disease), Physical Activity Scale for the Elderly, and smoking

Dam, Ewing, Ancoli-Israel et al, JAGS, 2008 56(9):1665-73

15

Sleep disturbance and cognition in older women (n=2932 women, mean age 83.5 years)

- Objectively measured (5-days actigraphy) disturbed sleep was consistently related to poorer cognition

	MMSE<26	Trails B >278s	P-value
SE<70%	1.61 (95% CI 1.20–2.16)	1.96 (95% CI 1.43–2.67)	<0.05
Higher sleep latency (30m)	1.23 (95% CI 1.13–1.33)	1.13 (95% CI 1.04–1.24)	<0.05
Higher WASO (30m)	1.15 (95% CI 1.06–1.23)	1.24 (95% CI 1.15–1.34)	<0.05

All analyses adjusted for age, race, depression, education, body mass index, health status, history of stroke, history of hypertension, functional status, smoking, alcohol use, caffeine, antidepressant use, and physical activity.

Blackwell, Yaffe, Ancoli-Israel et al, J Gerontol: MED SCI, 2006, 61A(4):405–410

16

Summary of Study of Osteoporotic Fractures Study Results (n= 3,022)

- A 30-40% increased risk of subsequent falls associated in older women with
 - TST < 7 hours / night
 - SE ≤ 65%
- An increased mortality risk in older women with
 - TST < 5 hours / night
 - SE ≤ 65%
 - >2 hour naps

After adjusting for race, age, BMI, medical conditions, depression, cognitive function, exercise, IADL, use of anti-depressant or benzodiazepine

Stone, K.L., Ewing, S.K., Lui, L.Y., Ensrud, K.E., Ancoli-Israel, S., et al. *JAGS* 54:1177-1183, 2006; Stone, K.L., Ancoli-Israel, S., Blackwell, T., et al. *Arch. Intern. Med.* :168(16):1768-1775:2008

17

Medications and Substances Associated with Insomnia

- Alcohol
 - Acute use
 - Withdrawal
- Caffeine
- Nicotine
- Antidepressants
 - SSRI
 - SNRI, atypical
- Corticosteroids
- Decongestants
 - Phenylpropanolamine
 - Pseudoephedrine
- β agonists, theophylline derivatives
- β antagonists
- Statins
- Stimulants
- Dopamine agonists

Any drug that crosses the blood brain barrier and affects a neurotransmitter system may be associated with insomnia

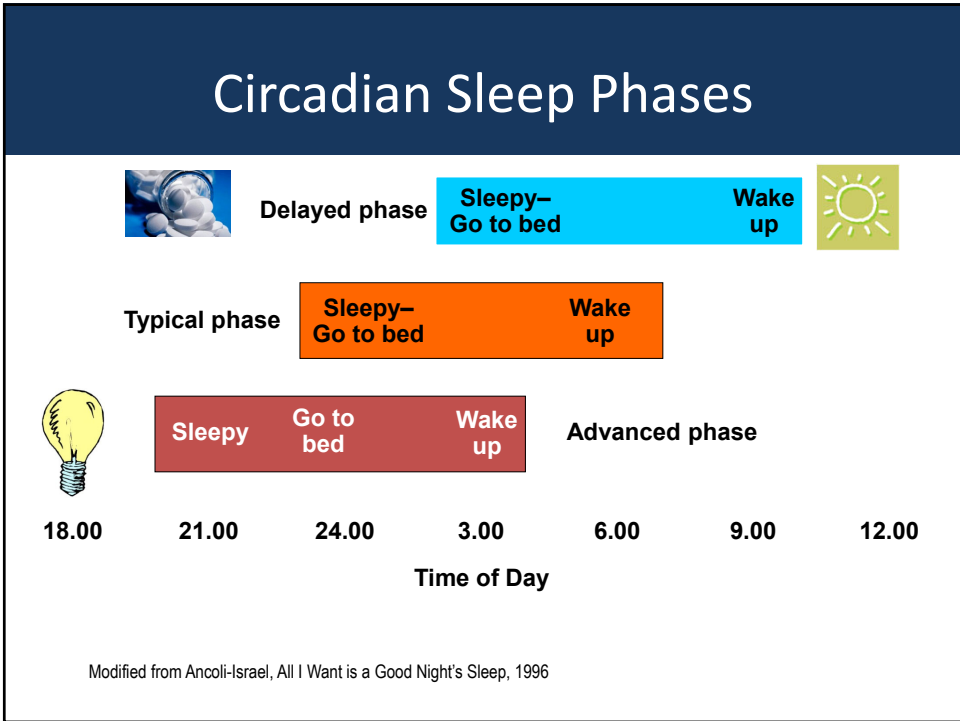
SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor; Schweitzer, PPSM.

Hauri P.J. Insomnia. *Clin Chest Med.* 1998;19:157-168. *A Special Report: Sleep Disturbance.* Boston, MA: Harvard Medical School Health Publications Group; 1999.

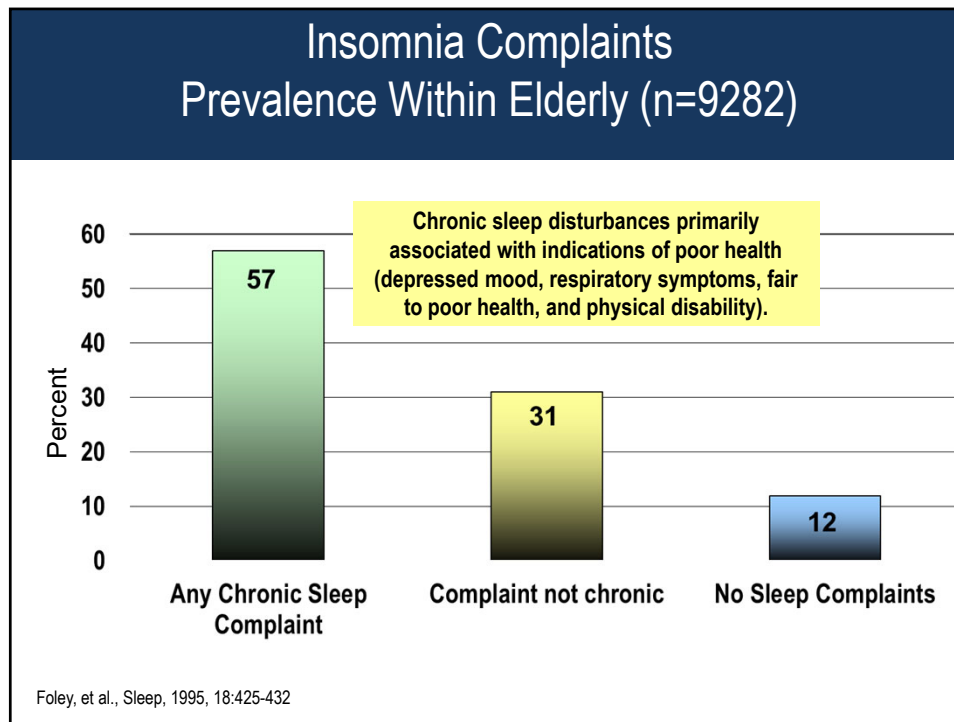
18

Circadian Rhythm Disturbance: “Early to bed, early to rise...”

19



20



21

Incidence of Insomnia in the Elderly

- Of the 2000 survivors with chronic insomnia at baseline, about 50% had no symptoms at follow-up
 - Improved self-perceived health associated with discontinuation of insomnia symptoms
- Foley et al concluded:
 - “...these data do not support a model of incident insomnia caused by the aging process *per se*.”

Foley D et al. Sleep. 1999;22:S366-372.

22

Treatment of Insomnia

- Cognitive Behavioral Therapy for Insomnia
 - First line treatment
 - Increase sleep drive
 - Optimize congruency between circadian clock and placement of sleep opportunity (time in bed)
 - Strengthen the signals from the circadian clock
 - Strengthen bed as cue for sleep (conditioned insomnia)
 - Reduce physiological arousal
- FDA approved sedative hypnotics

23

Choosing A Pharmacologic Therapy

(* = not DEA controlled)

- Do you have difficulty initiating or maintaining sleep (or both)?
- How many hours can you devote to sleep or inactivity, after taking the medication?

Agent	Initiates Sleep	Maintains Sleep	Sleep with limited opportunity	Required Inactivity
Eszopiclone (Lunesta)	√	√		8+ hours
Zaleplon (Sonata)	√		√	4 hours
Zolpidem (Ambien)	√			7-8 hours
Zolpidem MR (Ambien CR)	√	√		7-8 hours
Zolpidem sublingual (Eduar)	√			7-8 hours
Zolpidem oral spray (Zolpimist)	√			7-8 hours
Zolpidem sublingual (Intermezzo)	√		√	4 hours
Ramelteon (Rozerem)*	√			-
Doxepin (Silenor)*		√		-
Suvorexant (Belsomra)	√	√		7 hours
Lemborexant (Dayvigo)	√	√		7 hours
Daridorexant (Quviviq)	√	√		7 hours

24

Sedating Drugs NOT Recommended For Insomnia

- Diphenhydramine
- Tiagabine
- Melatonin
- Trazodone
- Valerian

Sateia MJ et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults, Clin Sleep Med, 2017

25

Diphenhydramine and other antihistamines (H1-Receptor Antagonists)

Advantages

- Available OTC
- Low cost
- *Perceived* as "safer than sleeping pills"

Disadvantages

- Hypnotic dose not well defined
- Tolerance within a week

Adverse Effects

- Sedation, grogginess
- Dry mouth, blurred vision, urinary retention
- Psychomotor impairment, dizziness, incoordination
- Delirium
- Renal failure
- Inattention
- Disorganized speech
- Altered consciousness
- Abnormal psychomotor activity
- Altered sleep/wake cycle (inc awakenings and naps)
- Behavioral disturbance

Agostini et al, Arch Intern Med, 2001, 161:2091-97

26

Sleep Disordered Breathing

27

Prevalence of OSA in Older Adults

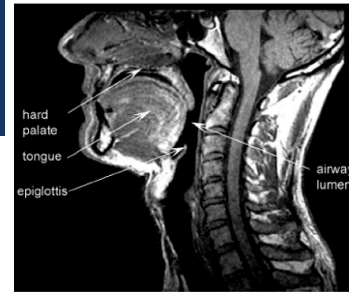
- One of the earliest studies to examine OSA in older adults (n=427; >65y/o) found a prevalence of 62% at RDI>10
- A much larger study of older men (MrOs; n=2911; age 76y) found that
 - 26.4% had RDI \geq 15; 60% had RDI \geq 5
 - The prevalence of RDI>15 increased with increasing age quartile (p=0.005)
 - The prevalence of RDI>5 did not increase with increasing age quartile (p=0.68)
- A more recent large study of community-recruited adults found that
 - for those aged 60-85 years (n=902), 48.7% had an RDI \geq 15 (64.7% in men, 35.2% in women)
 - significantly higher than in younger adults

Ancoli-Israel S et al Sleep, 1991, 14(6):486-495; Mehra R et al. JAGS 55:1356-1364, 2007; Heinzer, R et al Lancet Respir Med. 2015; 3(4): 310-318

28

Changes in airway anatomy with age - MRI findings

- Soft palate gets longer
- Pharyngeal fat pads increase in size
- Shape of bony structures around pharyngeal airway change
- Response of genioglossus muscle to negative pressure stimulation diminishes



Midsagittal magnetic resonance image illustrating anatomic structures of interest



Figure 2 Axial magnetic resonance image illustrating structures relevant to pharyngeal collapse.

Malhotra et al. *Am J Med*, 2006. 119:72.e9-e14

29

SDB+EDS = Mortality Risk

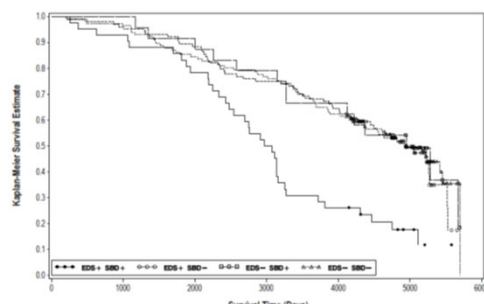


Figure 2—Survival curve as a function of excessive daytime sleepiness (EDS) and sleep-disordered breathing (SDB) status. Solid line: EDS+ SDB-. Dashed line: EDS+ SDB+. Long-short dashed line: EDS- SDB-. Dotted line: EDS- SDB+. Dark circles: censored EDS+ SDB+. Open circles: censored EDS+ SDB-. Open squares: censored EDS- SDB+. Open triangles: censored EDS- SDB-.

- The presence of SDB is an important risk factor for mortality from EDS in older adults.
- In the presence of SDB at $AHI \geq 20$, EDS was associated with an increased all-cause mortality risk in older adults, even when adjusting for other significant risk factors, such as prolonged sleep duration.
- In older patients who had SDB without EDS, or EDS without SDB, there was no increased all-cause mortality rate.

Gooneratne NS; et al Sleep disordered breathing with excessive daytime sleepiness is a risk factor for mortality in older adults. *SLEEP* 2011;34(4):435-442.

30

Is OSA pathological in elderly?

- ??? Most studies suggest that OSA does not increase the risk of mortality in the older adult
- Most studies DO suggest that older adults with SDB are
 - excessively sleepy
 - that OSA contributes to
 - decreased quality of life
 - greater risk of nocturia, hypertension and cardiovascular disease
 - decreased cognitive function

#

Launois SH, et al. Sleep apnea in the elderly: a specific entity? Sleep Med Rev 2007; 11(2).

31

Association with OSA: Cognition SOF (n = 400; age 82.8y)

- Cross sectional study of older women
- OSA associated with cognitive impairment (MMSE)
 - AHI \geq 15
 - OR 1.4, 95% CI 1.03-1.9
 - AHI \geq 30
 - OR 3.4, 95% CI 1.4-8.1
 - SaO₂ nadir<80%
 - OR 2.7, 95% CI 1.1- 6.6].14
- Each standard deviation increase in AHI was associated with 70% greater odds of cognitive impairment.

Spira AP et al Sleep-disordered breathing and cognition in older women. J Am Geriatr Soc 2008;56:45-50.

32

Older women with OSA have an increased risk of developing cognitive impairment – Prospective Study

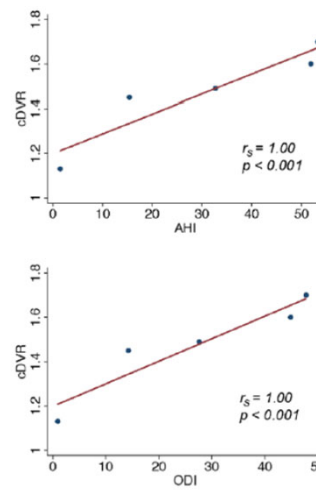
- Compared women
 - with OSA (n=105; 35.2%)
 - without OSA (n=193)
- At 5-year follow-up, those with OSA were more likely to develop MCI or dementia
 - 31.1% [n=60] vs 44.8% [n=47]; adjusted OR, 1.85; 95% CI, 1.11-3.08
- Elevated SaO₂ (>15 events/hour) and high % of TST (>7%) with apnea or hypopnea were associated with risk of developing
 - MCI (AOR, 1.71 [95% CI, 1.04-2.83])
 - dementia (AOR, 2.04 [95% CI, 1.10-3.78])
- Measures of sleep fragmentation (arousal index and wake after sleep onset) or sleep duration (total sleep time) were not associated with risk of cognitive impairment

Yaffe, K et al. JAMA. 2011;306(6):613-619

33

OSA and β -amyloid Burden in Older Adults

- Baltimore Longitudinal Study of Aging, neuroimaging substudy; Pilot study
 - 13 older adults (8 with normal cognition and 5 with mild cognitive impairment)
 - neuropsychological testing, PSG, A β imaging
- Results: Among participants with MCI, higher AHI and oxygen desaturation index were associated with greater A β deposition
 - There were no significant associations between OSA and A β deposition among cognitively normal participants.
 - There were no significant associations between sleep duration or sleep fragmentation and A β deposition
- **Conclusion:** These preliminary results suggest that among older adults with mild cognitive impairment, greater OSA severity is associated with greater A β deposition.

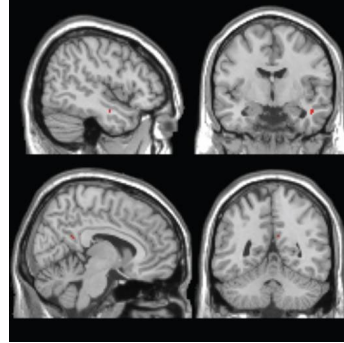


Spira A et al. SAGE Open Med. 2014 Aug 12;2. doi: 10.1177/2050312114546520

34

OSA associated with increased A β pathology

- PET from cognitively-normal adults with (n=19) and without OSA (n=19).
 - age 50-65 years
- Conclusion: OSA accelerates amyloid deposition and may contribute to the development or progression of Alzheimer's disease



Yun CH et al. J Alzheimers Dis. 2017;59(1):21-29

35

Does treating sleep apnea *in the older adult* lead to improvements?

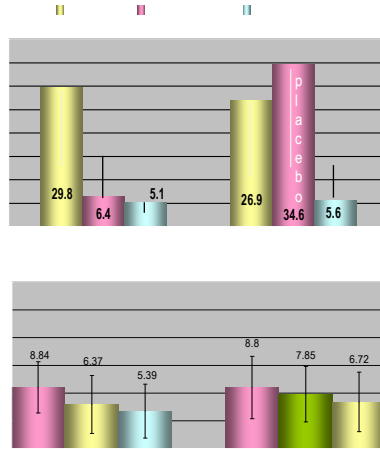
- In a review of the literature, Weaver and Chasen conclude that data suggest that in the elderly, CPAP
 - Reduces or eliminates apneas and hypopneas
 - Improves sleep architecture
 - Improves daytime sleepiness
 - Improves self-reported symptoms (snoring and gasping)
 - Improves motor speed and nonverbal learning and memory#
 - Improves vascular resistance, platelet coagulability and other factors affecting cardiac function#
 - Has a positive effect on nocturia, reducing the number of voids per night.

Weaver TE, Chasens ER. Continuous positive airway pressure treatment for sleep apnea in older adults. Sleep Med Rev 2007; 11(2)

36

Effect of CPAP in Alzheimer's Disease

- 3-weeks of CPAP in AD results in improvement in
 - AHI levels and ↓SpO₂
 - Epworth Sleepiness scores
 - Deeper Sleep
 - ↓N1, ↑N2,REM;
 - ↓WASO, ↓Arl, Improved cognitive functioning
 - Longer use slowed dementia progression



Ayalon et al. AJGP 2006 14(2):176-80; Chong et al JAGS 2006 54(5):777-81; Cooke, JR. et al. Sleep Med. 2009;10(10):1101-6; Ancoli-Israel,S., et al JAGS. :2008, 56:2076-81

37

Studies effect of CPAP on Cognition

- “CPAP may be effective in improving cognition, particularly in the presence of sleepiness and given good treatment adherence.
- CPAP treatment also shows promise for delaying further cognitive decline in those with MCI and AD
 - more cognitive assessments where encoding and recall are separated by a period of sleep are needed to understand OSA-related impaired cognition within individuals.”

Mullins A et al Neurobiology of Disease 145 (2020) 105054

Author	Study Design	Population	Age Range	Sex % Female	Cognitive Outcome or Risk
Chong et al. 2006	Randomized, controlled trial	AD	70-80	No	MMSE, ADL
Ayalon et al. 2006	Randomized, controlled trial	AD	70-80	No	MMSE, ADL
Cooke et al. 2009	Randomized, controlled trial	AD	70-80	No	MMSE, ADL
Mullins et al. 2020	Randomized, controlled trial	MCI and AD	70-80	No	MMSE, ADL

38

When to Treat Sleep Apnea in the Elderly?

- The bottom line is that if the sleep apnea is associated with clinical symptoms, then it should be treated, regardless of the age of the patient.
 - Excessive daytime sleepiness
 - Hypertension
 - Cognitive dysfunction
 - Nocturia
 - Cardiac disease
 - High levels of sleep-disordered breathing

Ancoli-Israel, Sleep Med Rev. 2007 Apr;11(2):83-5.

39

REM Behavior Disorder: Case Example

A 60-year old surgeon began to punch and kick his wife and jump out of bed during nightmares of being attacked “by criminals, terrorists, and monsters who always tried to kill me.” Work-related stress was the presumed cause of his sleep disturbance, but the violent behaviors intensified despite retirement 3 years later. He sustained several head lacerations, and his wife once had a severe headache for 2 days after receiving an accidental blow to the ear. The proper diagnosis was established after 11 years. A prodrome of excessive limb and body jerking during sleep had been present for at least 33 years.

Principles and Practice of Sleep Medicine, 1994



40

Treatment of RBD

- Neurological exam
- Pharmacological Treatment
 - Clonazepam* – effective in ~90% of patients
 - 0.25-0.5mg at bedtime
 - Tolerance generally does not develop
 - Discontinuation = immediate relapse
 - Mechanism of action unknown
 - Melatonin*
 - One hour before bedtime
 - starting at 6mg; increasing to 12-15 mg
- Behavioral treatment

41

Restless Legs Syndrome

- Restless Legs Syndrome
 - Feelings of “creepy/crawling” sensations in legs
 - Relieved only with movement

42

Screening Questions

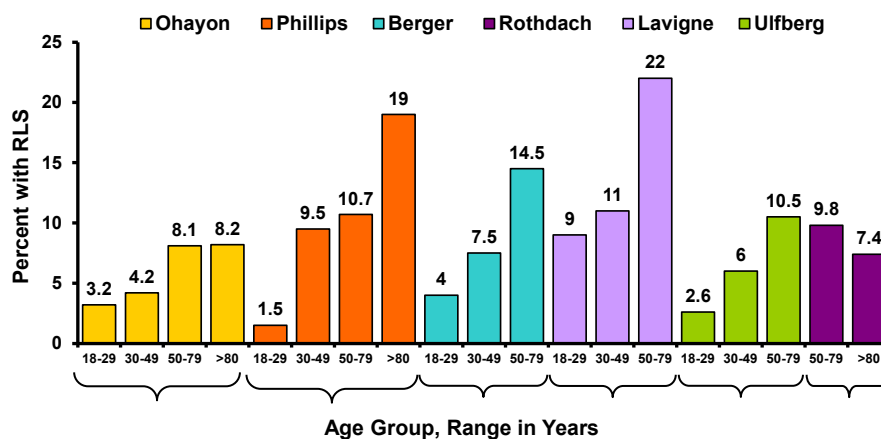
If you answer *YES* to *ALL* 4 Questions...

1. Do you have, or have you sometimes experienced, recurrent, uncomfortable feelings or sensations in your legs while sitting or lying down?
2. Do you have, or have you sometimes experienced, a recurrent need or urge to move your legs while sitting or lying down?
3. Do these uncomfortable feelings or sensations in your legs, or the need or urge to move, disappear/improve when you are active or moving around?
4. Are these uncomfortable feelings, or this urge to move, worse in the evening or at night compared with the morning?

Allen et al. Arch Int Med 2005 165(11):1286-92

43

Prevalence of RLS by Age



Ohayon M & Roth T. J Psychosom Res 2002, 53:547-554; Phillips B et al. Arch Intern Med. 2000, 160:2137-2141; Berger K et al. Arch Intern Med. 2000, 164:196-202; Rothdach AJ et al. Neurology. 2000, 54:1064-1068; Lavigne G & Montplaisir J. Sleep, 1994, 17:739-743; Ulfberg J et al Mov Disord. 2001, 16:1159-1163

44

Treatment for RLS

- Dopamine Agonists
 - ropinirole (Requip) 0.5-4 mg
 - pramipexole (Mirapex) 0.125-.5 mg
- Horizant (Gabapentin enacarbil extended-release tablets)
 - 600 mg once daily taken with food at about 5 p.m
 - For moderate-severe RLS
- Iron supplements
 - If Ferritin <50 – first line treatment
 - 325mg 1-2x/day
- Lifestyle changes and activities may provide some relief for mild to moderate RLS:
 - Avoid or decrease the use of alcohol, nicotine, and caffeine
 - Change or maintain a regular sleep pattern
 - Try moderate, regular exercise
 - Massage the legs or take a warm bath
 - Apply a heating pad or ice pack
 - Do aerobic and leg-stretching exercises of moderate intensity

Hening et al. *Sleep*. 2004;27:560-583.
Littner et al. *Sleep*. 2004;27:557-559.

45

Treatment for RLS

- Medications that make RLS worse:
 - Over-the-counter sleeping pills
 - Antihistamines (such as Benadryl, NyQuil, and Dimetapp)
 - Anti-nausea medications (such as Antivert, Compazine, and Dramamine)
 - Calcium channel blockers (used for high blood pressure and heart problems)
 - Antidepressants (such as Prozac, Effexor, and Lexapro)
 - Antipsychotics (used for bipolar disorder and schizophrenia)

46

Summary of Key Points – The Bottom Line

- It is not aging per se that results in poor sleep but rather all the things that go along with aging.
- Although the need to sleep does not change, the ability to sleep does change with age.
- Poor sleep in the older adult is most often associated with medical and psychiatric illness, medication, circadian rhythm changes and primary sleep disorders.
- No matter the age of the patient, sleep disorders should be treated if they are interfering with quality of life or if there is a medical risk associated with it.

47

Summary of Key Points – The Bottom Line (con't)

- The relationships between sleep/circadian dysfunction and neurodegenerative processes are bidirectional
 - Sleep and circadian disruption increase the risk of MCI and AD
 - Sleep and circadian disruption are common in AD
 - Behavioral, physiological and molecular markers of circadian system function suggest progressive deterioration of sleep and circadian rhythmicity as the AD progresses
- OSA increases the risk of MCI and AD
 - OSA treatment studies suggest that cognition may improve, but more studies are needed
- Because late-life sleep disturbance can be treated, interventions to improve sleep or maintain healthy sleep among older adults may help prevent or slow AD to the extent that poor sleep promotes AD onset and progression.

48

Aging seems to be the only available way to live a long life

Daniel Francois Esprit Auber