Neurology and Sleep
A to Z in 20 minutes

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FAAN FAASM

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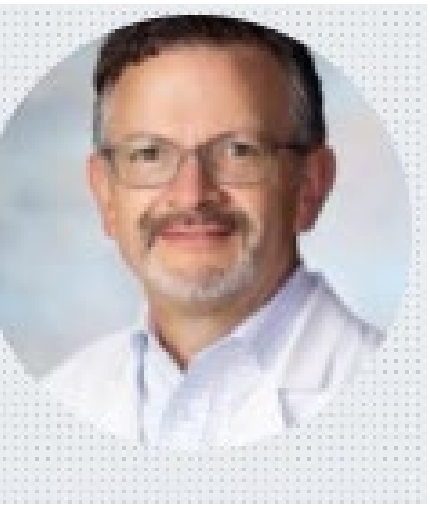
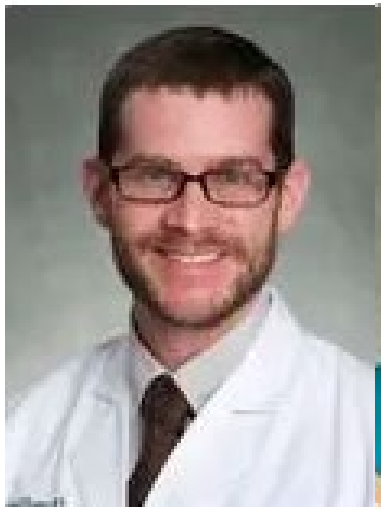
Disclosures

- I have no disclosures as it pertains to this talk

- Last commercial speaking engagements greater than 5y ago as speaker for Acadia pharmaceuticals for Nuplazid





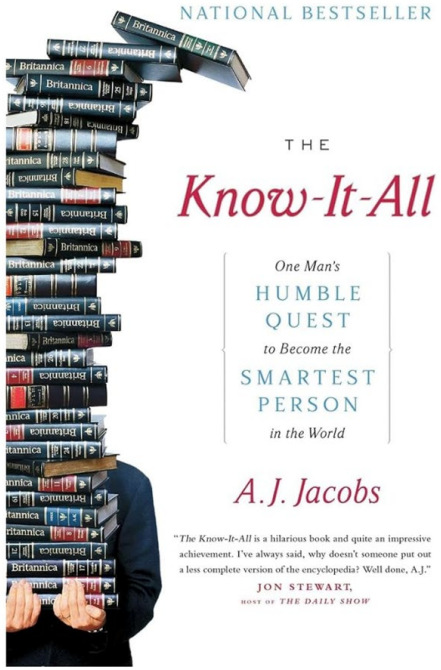
Adam Foreman MD

Virginia Kellner MD

Shail Thanki MD

OSA

A Age, alcohol, Alzheimer's ds
B Bruxism
C Caffeine/adenosine, Cancer, Carpal tunnel syndrome, circadian, Cluster HA, CPAP
D Diabetes
E EEG, Epilepsy, Epworth Sleepiness Scale; eugeroic
F fibromyalgia
G ghrelin
H sleep Hygiene, hypothalamus
I insomnia, INSPIRE, inflammation
J Joe (the fat boy from Pickwick papers)
K Kleine Levin syndrome
L lark vs owl; Leptin
M migraine; MS
N narcolepsy; nicotine; night terrors; 2017 Nobel prize
O orexin; OSA;
P Parkinson's 'PD'; PLMD; PDEi
Q Quviviq etc
R REM Behavior d.o. 'RBD'; RLS
S shift work; stroke
T telomeres
U uvula; UPPP; UARS
V valerian
W Wisconsin sleep cohort study
X eXercise
Y youth
Z z drugs; zeitgebers; zhuzh



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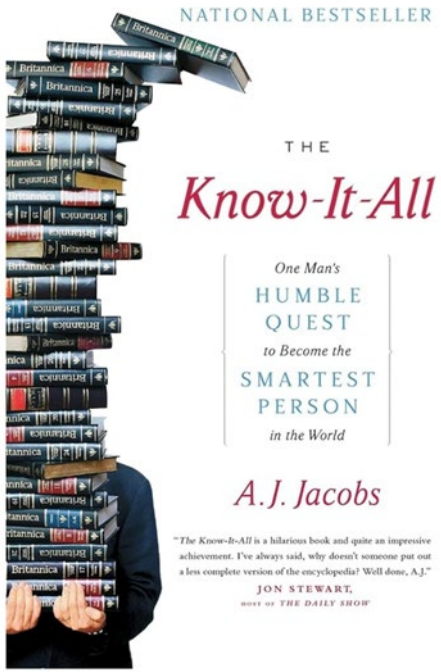

Ambitious
or
Asinine
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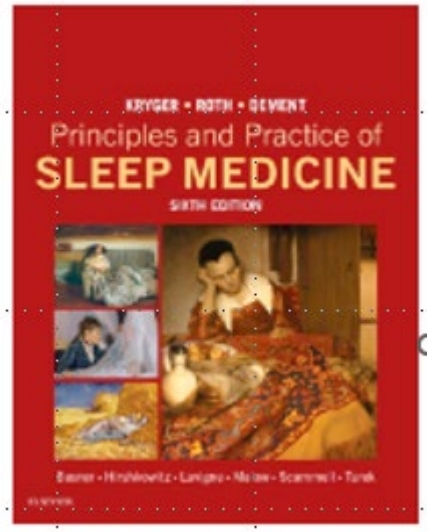
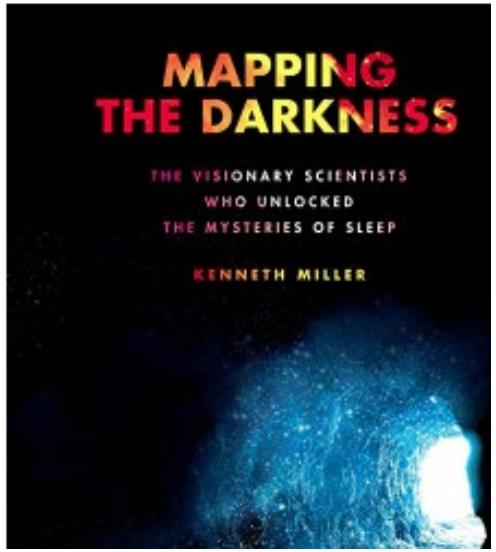
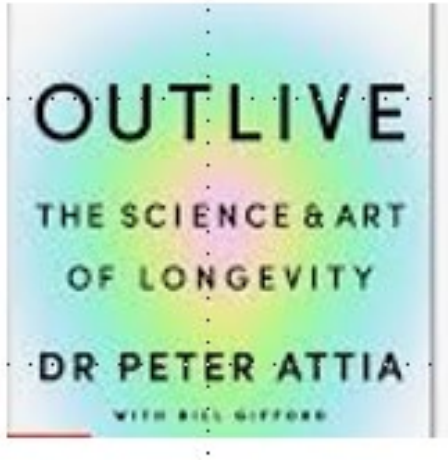
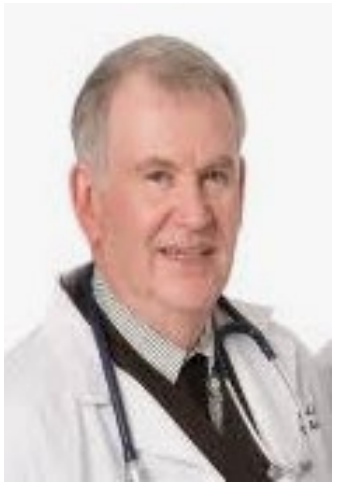
Witless
Yeasty
Zany
Here
goes…



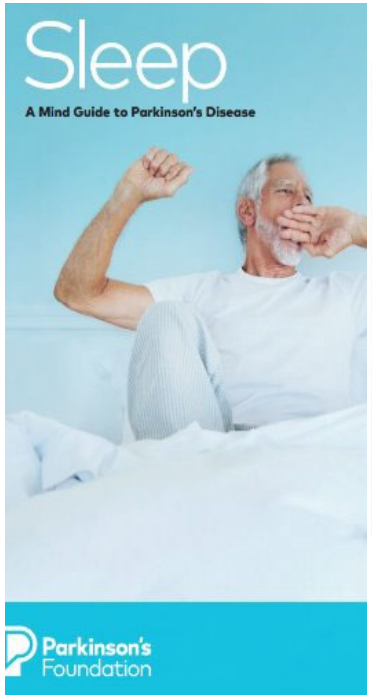


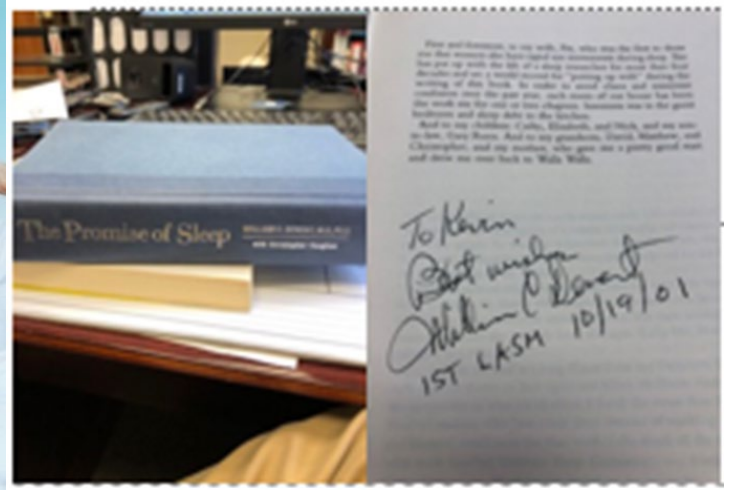


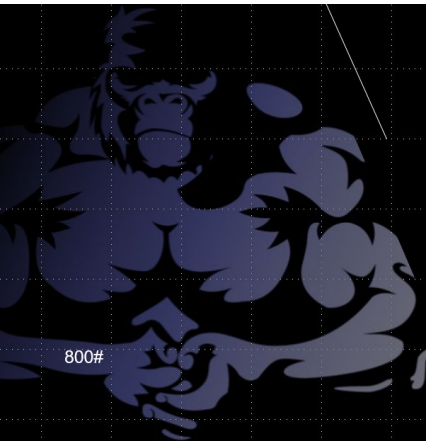


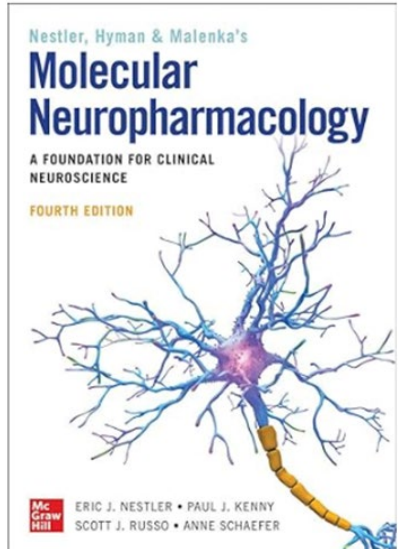
JY Bordelon, MD

J Rao, MD 1943-2019









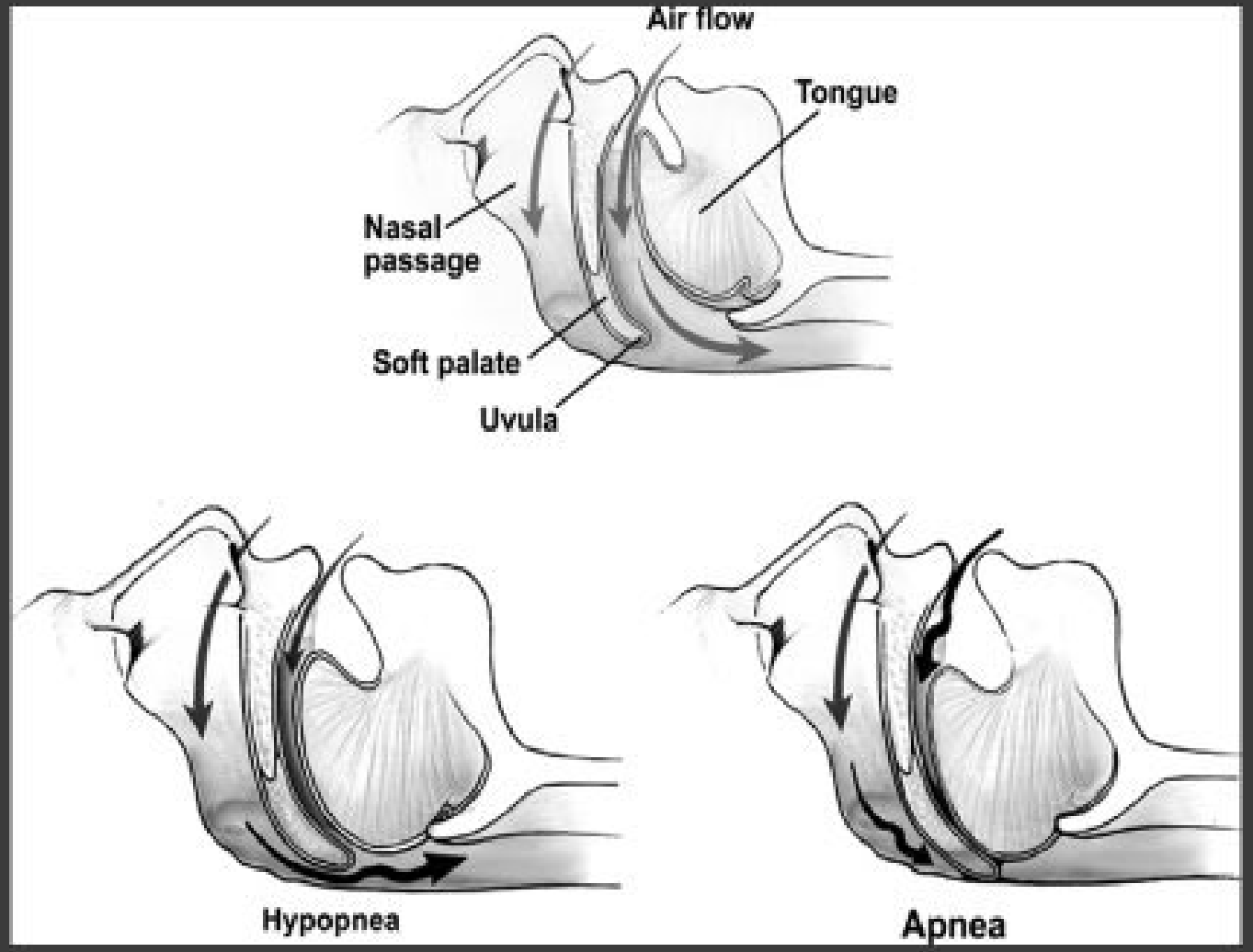
Obstructive sleep apnea (OSA)

800#

I love you so much.
Except when you snore and then I just want to punch you in the face.
ecards

800#

Partial and complete airway obstruction resulting in hypopnea and apnea, respectively



Somers, V. K. et al. J Am Coll Cardiol 2008;52:686-717

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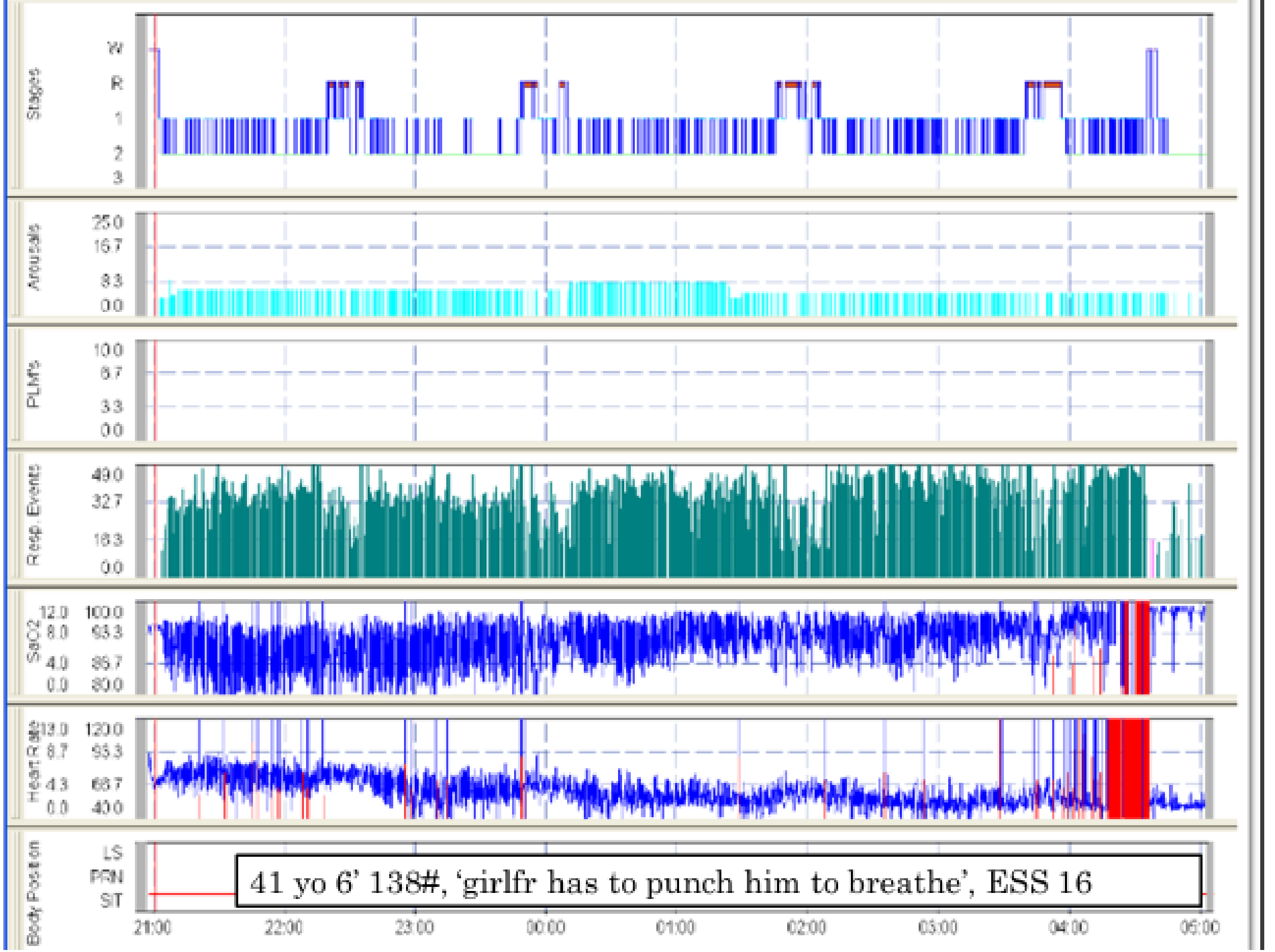
Stages
W
R
1
2
3
Arousals
250
167
83
00
PLMs
100
67
33
00
Resp. Events
490
327
163
00
SpO2
12.0 100.0
8.0 93.3
4.0 86.7
0.0 80.0
Heart Rate
13.0 120.0
8.7 93.3
4.3 66.7
0.0 40.0
Body Position
LS
PRN
SIT
41 yo 6' 138#, 'girlfr has to punch him to breathe', ESS 16
21:00
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File New Config Options Help
Stages
Time: 80:55
Stages
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Heart Rate
13.0
8.7
4.3
0.0
120.0
93.3
66.7
40.0
Body Position
LS
PRN
SIT

AHI (apnea hypopnea index)

Apnea (lack of breath)

Hypopnea (shallow breath accompanied by desaturation of O2)

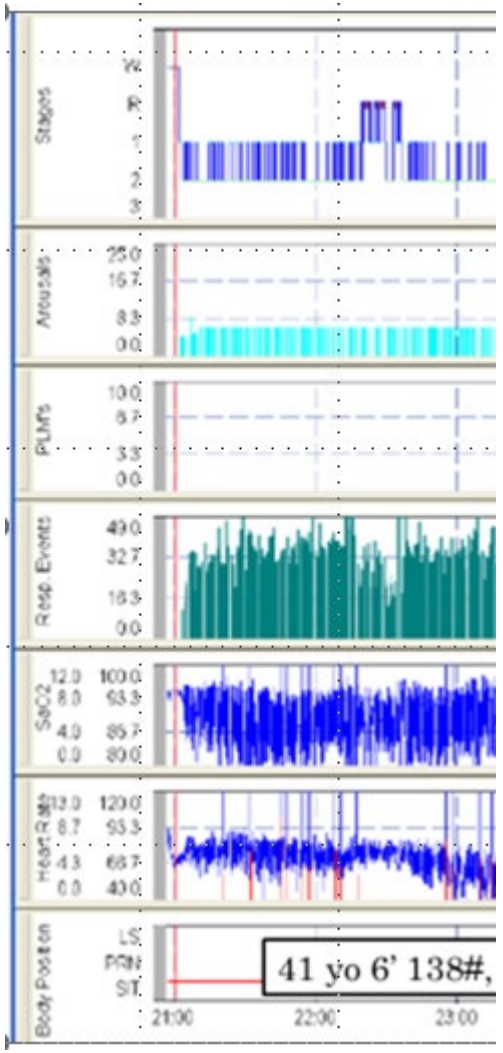
‘AHI’

Normal 0-4/hour

Mild obstructive sleep apnea 5-14/hr

Moderate OSA 15-29/hr

Severe OSA >30/ hr



Obstructive sleep apnea (OSA)

Table 114-2

Medical and Mental Health Conditions for Which There Is Evidence of Association with Obstructive Sleep Apnea*

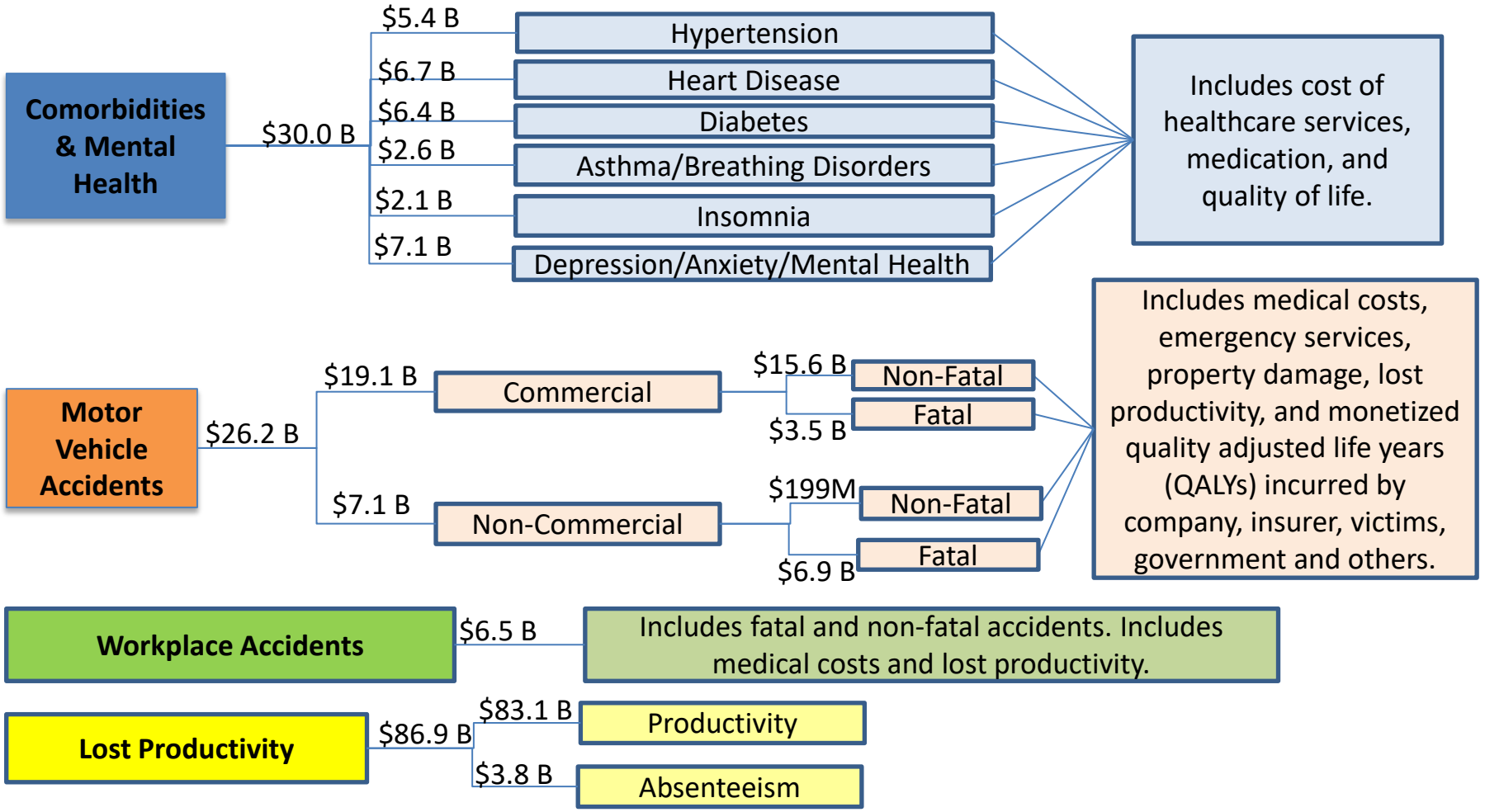
Hypertension [155] (25% to 50% all hypertension; as high as 83% in drug-resistant hypertension)
Myocardial infarction [156] (as high as 70%)
Stroke [157] (as high as 68%)
Depression [158]
Congestive heart failure [159] (as high as 76%)
Asthma [51]
Chronic obstructive pulmonary disease [48] (as high as 50%)
Atrial fibrillation (and other dysrhythmia) [38] (49%)
Type 2 diabetes [46] (as high as 48%)
Traffic and industrial accidents [83] (as high as fivefold increase)
Overall mortality [160] (increased risk by 46%)

SLEEP Kryger et al

A series of observations from my sleep center 2016

- average Epworth 10
- 2/3 had HTN
- Nearly half of pt's had nadir O2 sat <80%, and 1/3 had >15 m of O2 <88%
- 1/5 had no REM and of those wo REM all had HTN
- of those wo REM, overall AHI's were twice as bad as their cohorts
- those wo REM also had less SWS [24minutes vs 80m]

Sources of Cost for Undiagnosed OSA



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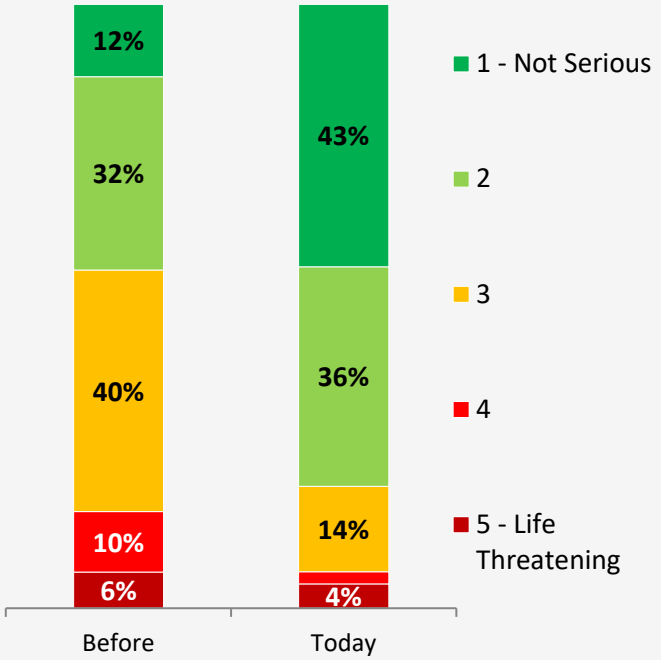
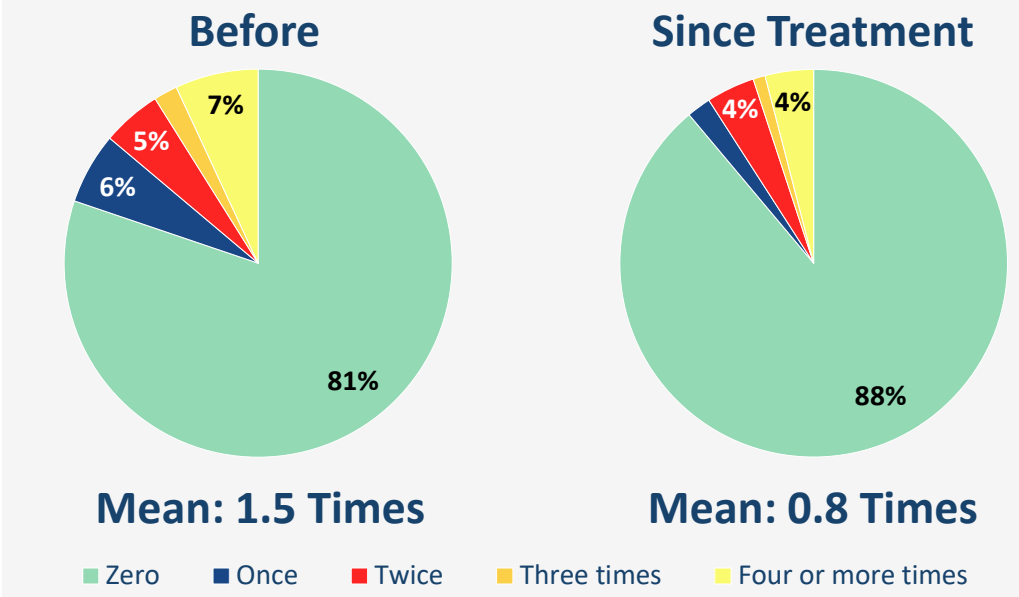
Hypertension Severity

Before and after sleep apnea treatment

Hypertension seriousness before and after treatment of OSA



Hospital visits for Hypertension



Base: n=288 (Percentages under 3% are not shown for transparency).

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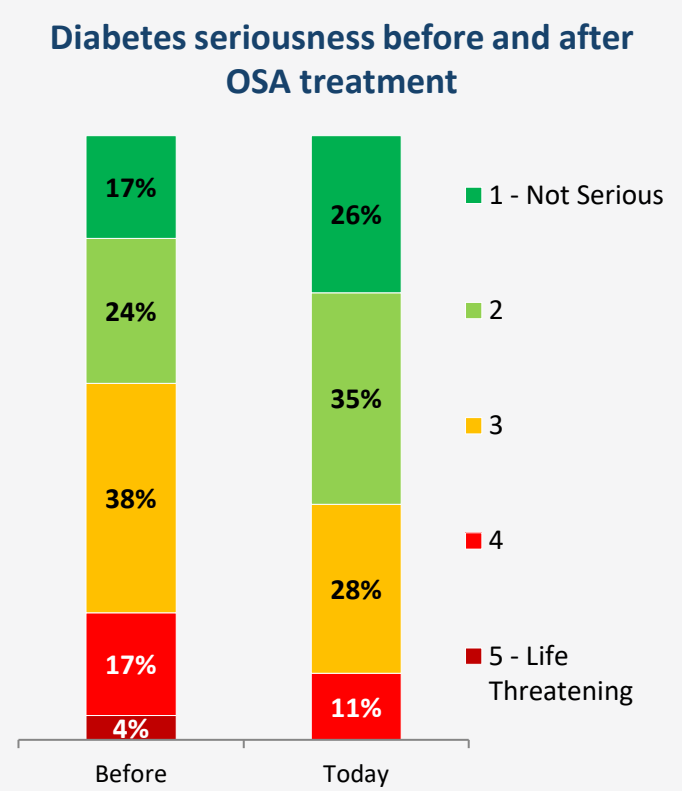
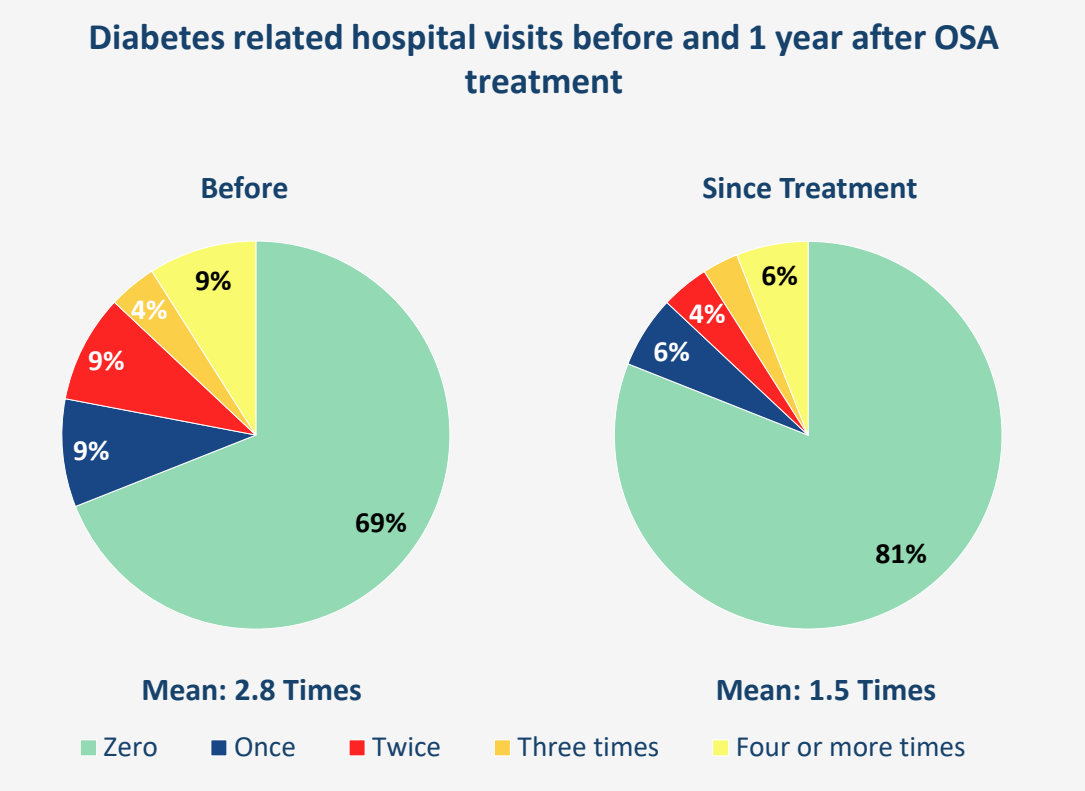
Diabetes Severity

Before and after sleep apnea treatment





Base: n=111 (Percentages under 3% are not shown for transparency).

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OSA Treatment Has a Major Impact on Comorbidities

After one year, patients surveyed state OSA treatment delivers…

Hypertension

- 41% report blood pressure improvement
- 17% report decrease in medication usage

Diabetes

- 31% report improved HbA1c
- 14x increase in “good quality” sleep

Asthma & Breathing Conditions

- 54% report improved respiratory function
- 70% increase in patients reporting symptoms as mild
- 8x increase in “good quality” sleep

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OSA Treatment Has a Major Impact on Comorbidities

After one year, patients surveyed state OSA treatment delivers…

Insomnia

- 7x increase in good quality sleep
- Decline from 54% to 1% reporting “very bad” quality sleep

Depression, Anxiety and Mental Health

- 12x increase in “good quality” sleep
- 4x reduction in reported life threatening mental health condition
- 49% report improved mental health

Heart Disease

- 56% report reduced heart disease risk
- 5x decrease in self-reported life-threatening heart disease
- Decline from 50% to 3% reporting “very bad” quality sleep
- Increase from 0% to 26% reporting “very good” quality sleep

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Benefits of Treatment: The "Triple Aim"

Beyond economics and cost savings, imagine what the U.S. would be like if all 29.4 million people with OSA received treatment…

Payors/ Employers

- Reduces costs long-term
- Increases productivity
- Lowers accident rates and liability costs

Patients

- Improves health and life expectancy
- Increases productivity
- Increases quality of life
- Improves relationships

Providers

- Aligns with population health incentives
- Improved outcomes increases profit in a value-based healthcare system
- Lowers healthcare utilization and reduces admissions

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Journal of Clinical Sleep Medicine → Volume 12, Issue 05

Free Access • CPAP

Justice Antonin Scalia —The Wrong Message

Nancy A. Collop, MD, FAASM

Published Online: May 15, 2016 •
https://doi.org/10.5664/jcsm.5778 • Cited by: 1

INTRODUCTION

I read with interest the reports that Justice Antonin Scalia was found dead in bed with his CPAP neither attached to him nor even plugged in. Many of the news reports noted that: "…the chance of death from skipping a single day is tiny, and patients can and do take breaks because they have a cold, forget to take the machine on a short trip or because the masks are irritating. Typically the only immediate ill effects are snoring and possibly getting up at night gasping."[1] But oh how I wished the message was different! Given Justice Scalia's reported comorbid illnesses and his probable severe sleep apnea (I am guessing his neck circumference at least 18+ inches), the likelihood that he died of either a cardiac arrhythmia, massive stroke or pulmonary embolism is quite high. We will never know if he wore his CPAP that night, would he be alive today, however it is likely that if he had been using his CPAP that night assuming the final event was a cardiovas event, there would have been a reduced likelihood of a mortal event.

JCSM | Journal of Clinical Sleep Medicine

ABOUT

INTRODUCTION

I read with interest the reports that Justice Antonin Scalia was found dead in bed with his CPAP neither attached to him nor even plugged in. Many of the news reports noted that: "…the chance of death from skipping a single day is tiny, and patients can and do take breaks because they have a cold, forget to take the machine on a short trip or because the masks are irritating. Typically the only immediate ill effects are snoring and pos getting up at night gasping."[1] But oh how I

Nancy Collop, MD, Master FCCP
Professor of Medicine

We don't want to use scare tactics to convince our patients to use their CPAP nightly. But for patients with cardiovascular risk factors like Justice Scalia, missing their CPAP for one night could set them up for increased risk of sudden death and stroke; perhaps even *taking it off early* may increase the risk since REM sleep is often later in the night and the most vulnerable stage of sleep for OSA patients. It has been shown that OSA patients are more likely to die of sudden death between the hours of 12 midnight and 6 AM,[3] and the more severe their hypoxemia, the higher their risk.[4] Additionally patients who suffer a "wakeup stroke" are more likely to have OSA.[5] And sleep apnea patients are also thought to be of increased risk for a pulmonary embolism.[6] Any of these catastrophic events could have happened to Justice Scalia and all have a potential relationship to his diagnosis of obstructive sleep apnea.

When a patient asks me "is it okay to miss using my CPAP?" my response is to reiterate th
whenever they don't use their CPAP, the
back to having sleep apnea—perhaps not as

JCSM | Journal of Clinical Sleep Medicine

ABOUT

When a patient asks me "is it okay to miss using my CPAP?" my response is to reiterate that whenever they don't use their CPAP, they go back to having sleep apnea—perhaps not as bad as when they were first diagnosed, but with a cumulative effect of worsening each night without it.[7] And if they have all the risk factors that Justice Scalia had—missing one night may be deadly. There is much we don't know about Justice Scalia's death however a better message surrounding his lack of CPAP use that night should have been about the importance of obstructive sleep apnea as a comorbid condition—not downplaying the unknown risk of not using CPAP for one night.

CITATION

Collop NA. Justice Antonin Scalia—the wrong message. *J Clin Sleep Med* 2016;12(5):639–640.

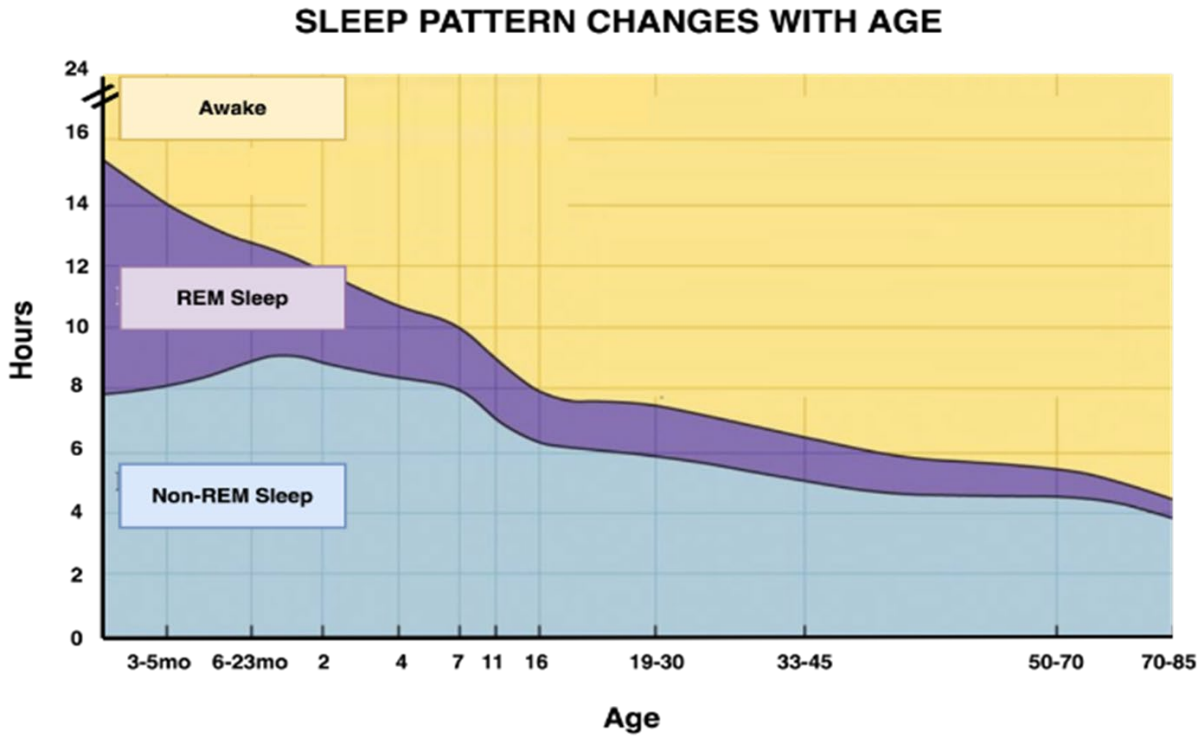
REFERENCES

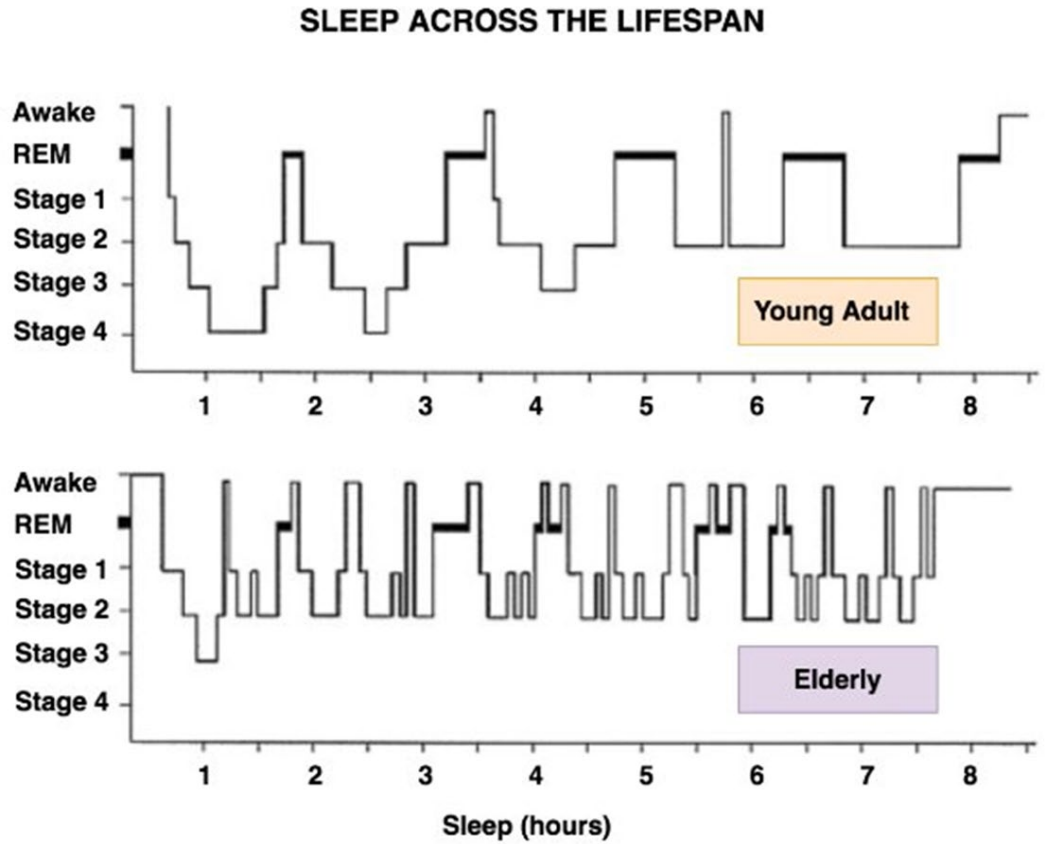
1 Cha AEDid sleep apnea contribute to Justice Scalia'
His unplugged breathing machine raises that questi
Accessed 3/10/16Available from:
https://www.washingtonpost.com/news/to-your-

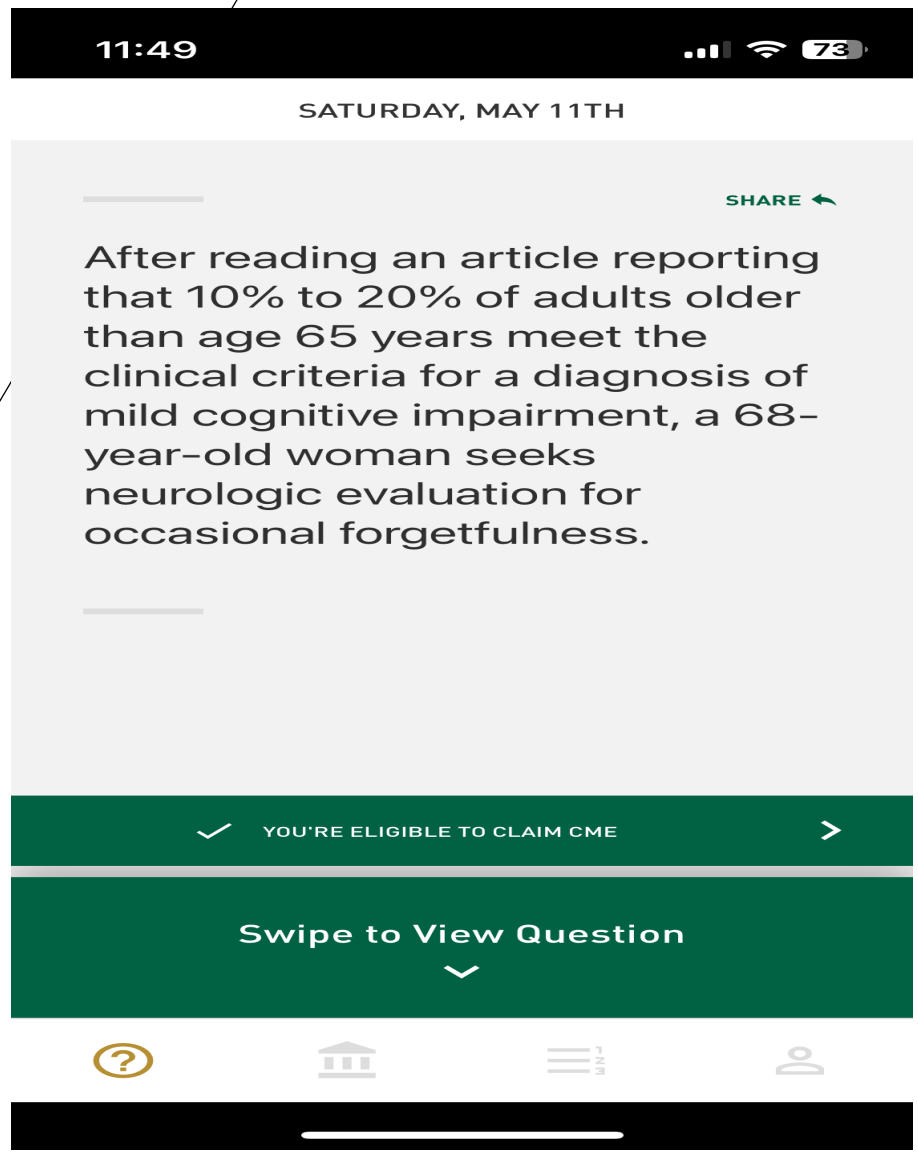
jcsm.aasm.org

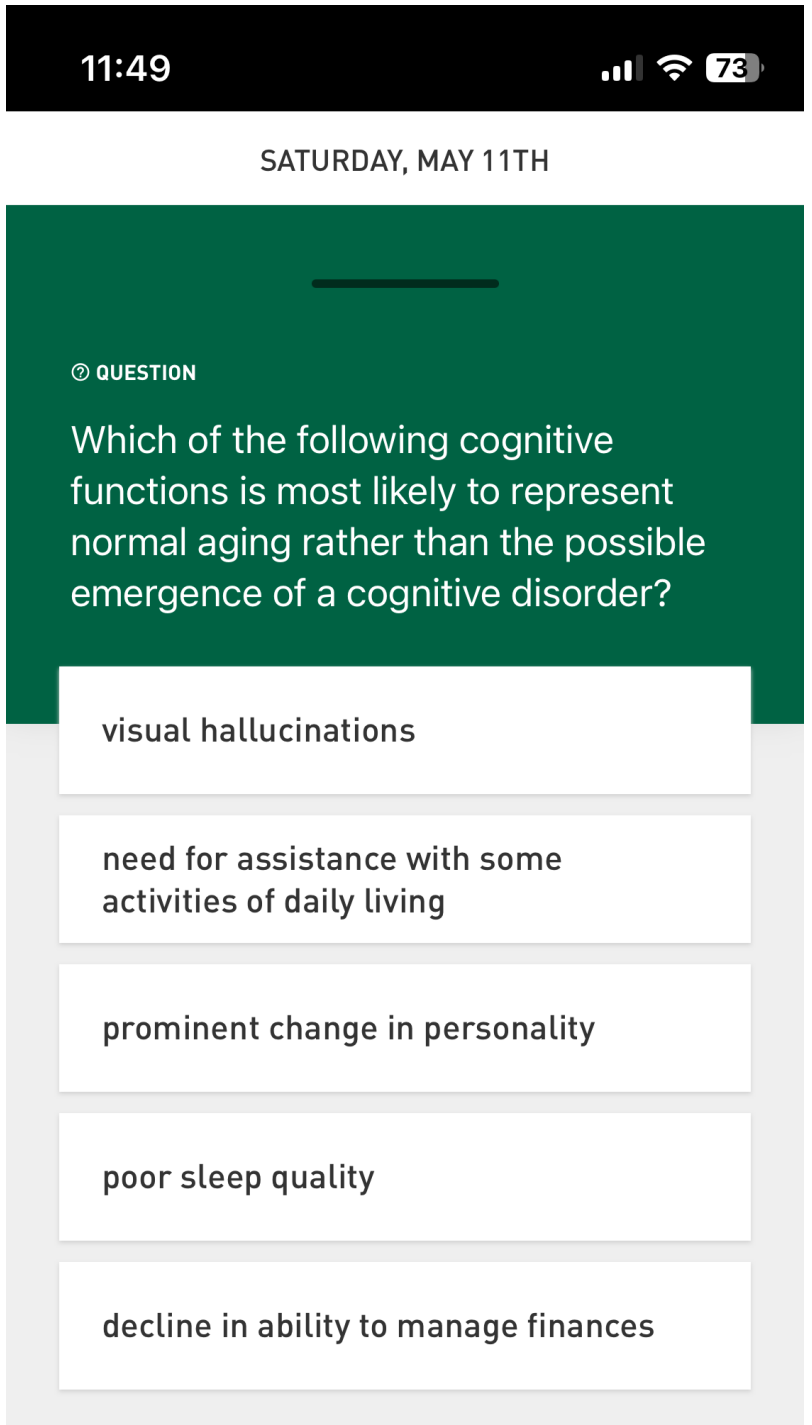
Nancy Collop, MD, Master FCCP
Professor of Medicine

AGE


SLEEP PATTERN CHANGES WITH AGE
Awake
REM Sleep
Non-REM Sleep
Hours
24
16
14
12
10
8
6
4
2
0
3-5mo
6-23mo
2
4
7
11
16
19-30
33-45
50-70
70-85
Age


SLEEP ACROSS THE LIFESPAN
Awake
REM
Stage 1
Stage 2
Stage 3
Stage 4
Young Adult
1
2
3
4
5
6
7
8
Awake
REM
Stage 1
Stage 2
Stage 3
Stage 4
Elderly
1
2
3
4
5
6
7
8
Sleep (hours)


11:49
73
SATURDAY, MAY 11TH
SHARE
After reading an article reporting that 10% to 20% of adults older than age 65 years meet the clinical criteria for a diagnosis of mild cognitive impairment, a 68-year-old woman seeks neurologic evaluation for occasional forgetfulness.
YOU'RE ELIGIBLE TO CLAIM CME
Swipe to View Question


11:49
73
SATURDAY, MAY 11TH
QUESTION
Which of the following cognitive functions is most likely to represent normal aging rather than the possible emergence of a cognitive disorder?
visual hallucinations
need for assistance with some activities of daily living
prominent change in personality
poor sleep quality
decline in ability to manage finances

THAT IS CORRECT

Rate

82% of peers answered this question correctly

Nonrestorative or interrupted sleep may accompany aging for a variety of reasons and cause cognitive inefficiency. It is important to screen patients with cognitive symptoms for reversible causes, including impaired sleep, depression, hearing loss, medication effects, or head trauma. Among the other options presented, visual hallucinations should arouse suspicion for a possible diagnosis of dementia with Lewy bodies. A prominent change in personality or behavior may signal frontotemporal dementia. Decline in the ability to manage finances or a need for assistance with other activities of daily

YOU'RE ELIGIBLE TO CLAIM CME

11:50

SATURDAY, MAY 11TH

BACK TO QUESTION OF THE DAY

assistance with other activities of daily living are frequent early features of a major neurocognitive disorder such as Alzheimer disease and when present should be further evaluated with formal testing of cognition.

visual hallucinations	0%
need for assistance with some activities of daily living	12%
prominent change in personality	0%
Your Answer: poor sleep quality	82%
decline in ability to manage finances	5%

11:50

SATURDAY, MAY 11TH

BACK TO QUESTION OF THE DAY

need for assistance with some activities of daily living	12%
prominent change in personality	0%
Your Answer: poor sleep quality	82%
decline in ability to manage finances	5%

REFERENCES

Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA. 2014;312(23):2551-2561.

alcohol / etoh

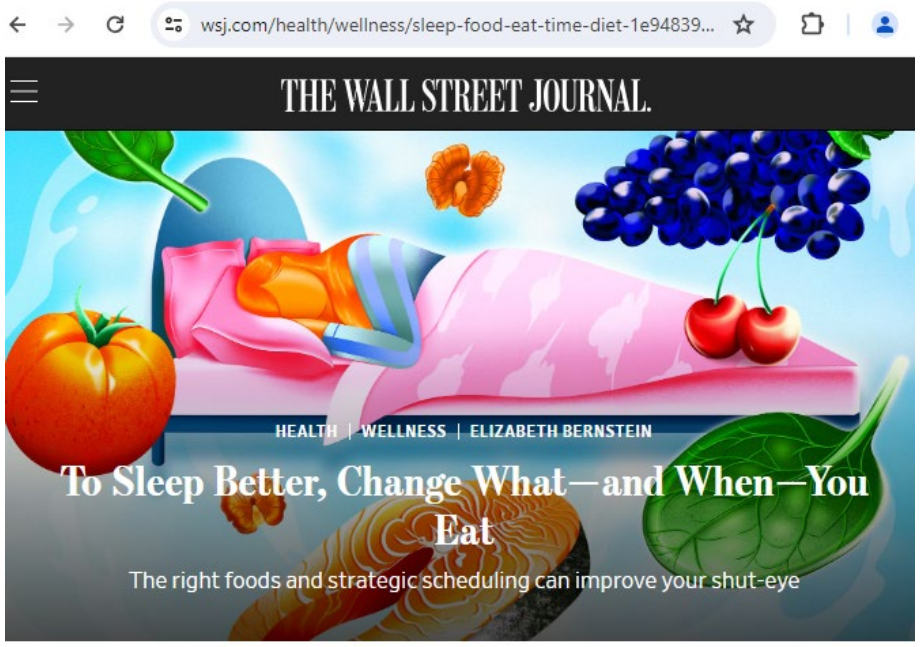


ILLUSTRATION: VIRGINIA GABRIELLI

By Elizabeth Bernstein Follow
April 30, 2024 8:00 am ET

Cut back on alcohol

Yes, alcohol may help you wind down at night and fall asleep faster. But it also messes with your sleep quality. (Do I really need to tell you this?) It suppresses REM sleep, causes sleep disturbances and shortens sleep duration, says Massachusetts General's Naidoo.

Alcohol probably impairs sleep quality more than any other factor we can control.

Don't confuse the drowsiness it produces with quality sleep.

Alzheimer's / dementia

Risk of dementia with sleep conditions:

- Chronic sleep deprivation <6hr was associated with a 30% increased risk of dementia Sabia. Nat Comm 2021

Alzheimer's / dementia

Risk of dementia with sleep conditions:

- Chronic sleep deprivation <6hr was associated with a 30% increased risk of dementia Sabia. Nat Comm 2021
- Obstructive sleep apnea 'OSA' associated with dementia

Alzheimer's / dementia

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- Chronic sleep deprivation <6hr was associated with a 30% increased risk of dementia Sabia. Nat Comm 2021
- Obstructive sleep apnea 'OSA' associated with dementia

Sleep conditions occurring **in dementia patients**:

- 50% of moderate to severe AD pt's have sleep disturbances

Alzheimer's / dementia

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- 50% of moderate to severe AD pt's have sleep disturbances
- AD pt's have reduced SWS, REM and incr arousals, N1

Alzheimer's / dementia / **Apo E**

Risk of dementia with sleep conditions:

- Chronic sleep deprivation <6hr was associated with a 30% increased risk of dementia Sabia. Nat Comm 2021
- Obstructive sleep apnea 'OSA' associated with dementia

Sleep conditions occurring **in dementia patients**:

- 50% of moderate to severe AD pt's have sleep disturbances
- AD pt's have reduced SWS, REM and incr arousals, N1

- An association has been also found between the ApoE-ε4 allele and OSA. Kadotani Jama 2001

Bruxism

- 13% of population
- Biological
- psychological
- exogenous

Caffeine

- Adenosine antagonist (similar structure)
- Half life 6 h
- Cup of coffee 100mg caffeine; over half of American adults drank >300mg caffeine daily
- May reduce SWS but REM unaffected

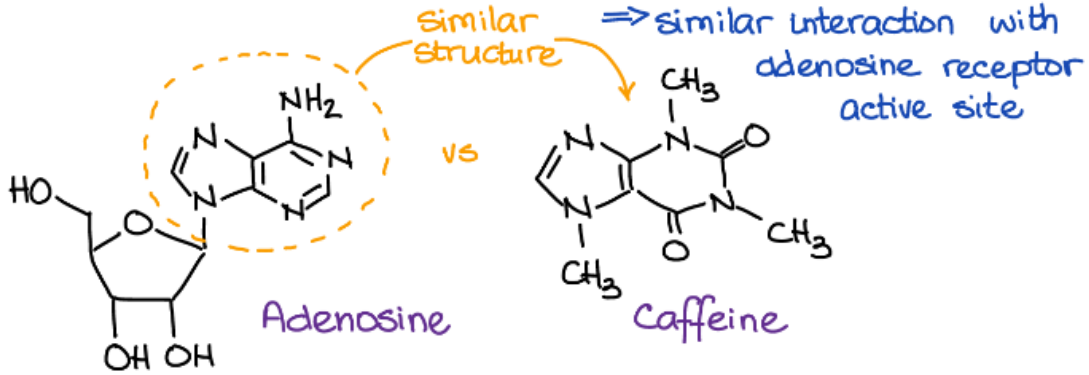
SLEEP 2017

- Wikipedia says a tablespoon size of pure powdered caffeine could be lethal

Adenosine

'an endogenous nucleoside'
inhibitory effect on Ach / so 'anticholinergic?'

a biomarker of sleepiness, accumulating during wakefulness in brain.



SECTIONS HOME SEARCH The New York Times

Study Suggests Genetics as a Cause, Not Just a Risk, for Some Alzheimer's

Lead in Beethoven's Hair Offers New Clues to Mystery of His Deafness

First Patient Begins S Therapy That F.D.A.

Well

BODY

Caffeine Powder Poses Deadly Risks

BY MURRAY CARPENTER MAY 18, 2015 12:30 PM

Murray Carpenter

A year ago, Logan Stiner of LaGrange, Ohio, was an honors student and prom king looking forward to his high school graduation. "He was burning the candle at both ends, because he had a couple of projects that he had to finish for finals," said his mother, Kate

In its pure form, caffeine is quite powerful. A teaspoon of caffeine powder is roughly equal to 16 to 25 cups of coffee. Ten grams, about a tablespoon, is a lethal dose for an adult. A 100-gram package — as much caffeine as 400 "tall" cups of Starbucks coffee, 1,250 Red Bulls, or 3,000 cans of Coke — costs about $10.

Logan Stiner The Logan Stiner Foundation

After the deaths, the Food and Drug Administration in July advised consumers to avoid the powder. "Pure caffeine is a powerful stimulant, and very small amounts may cause accidental overdose," the statement read.

151. ^ Carpenter M (18 May 2015). "Caffeine powder poses deadly risks". *New York Times*. Archived from the original on 25 January 2022. Retrieved 18 May 2015.

Cancer

- Deranged or insufficient sleep could increase one's cancer risk via an immune dysregulation link
- Some studies show increased breast ca risk with night shift or alternating shift work SLEEP 2017

Carpal Tunnel Syndrome

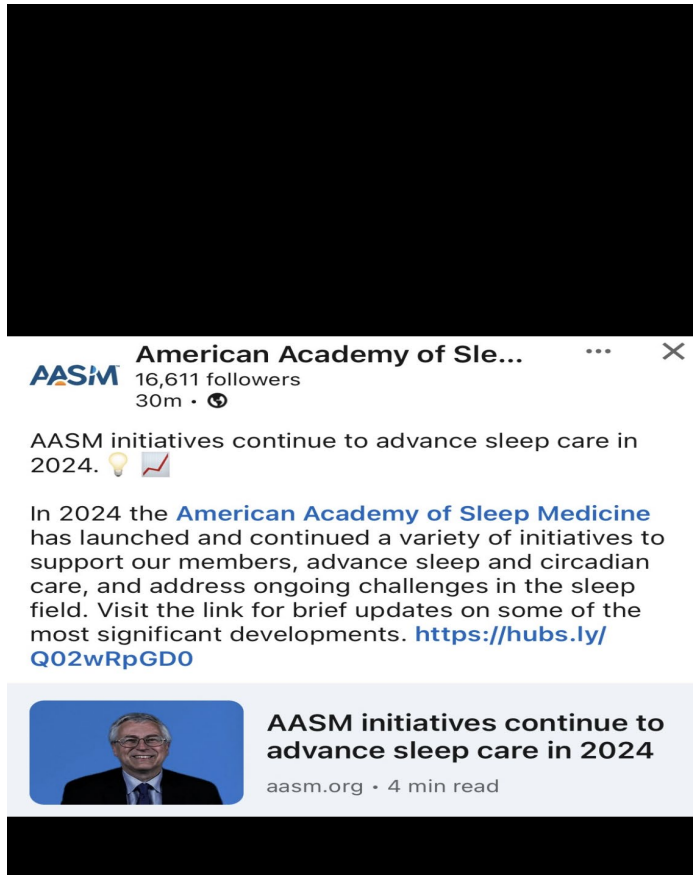
- Symptoms often manifest during sleep

- More common in pregnancy during sleep in part due to relaxin, and of course maybe in part due to weight gain

SLEEP 2017

Circadian

- About a day
- Aasm messages now talk about sleep and ‘circadian’ care



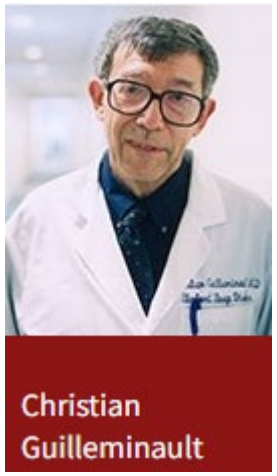
Cluster HA

- 01-03 am
- Cluster pt's have both an advance and a decrease in amplitude of melatonin secretion Pringsheim Can J Sci 2002

CPAP

- Colin Sullivan had the idea for cpap after watching an endoscopic video by Christian Guilleminault
- 1980
- Vacuum cleaner motor

Colin Sullivan with his early CPAP machine in 1984. About 1000 patients used the machine. PAUL MATTHEWS



1938-2019

Diabetes

Brazilian Journal of Medical and Biological Research (2008) 41: 180-187
ISSN 0100-879X Review

The reciprocal interaction between sleep and type 2 diabetes mellitus: facts and perspectives

R.C. Martins, M.L. Andersen and S. Tufik

Departamento de Psicobiologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brasil

Correspondence to: M.L. Andersen, Departamento de Psicobiologia, EPM, UNIFESP, Rua Napoleão de Barros, 925, 04021-002 São Paulo, SP, Brasil
Fax: +55-11-5572-5092. E-mail: mandersen@psicobio.epm.br

Type 2 diabetes mellitus is a systemic disease characterized by intolerance to glucose and peripheral resistance to insulin. This endocrine disease affects fundamental mechanisms of the central nervous system and jeopardizes the balance of vital functions such as the cardiovascular and circadian rhythm. The increased prevalence of metabolic disorders in our society is aggravated by endemic voluntary postponement of bedtime and by the current sedentary lifestyle, leading to epidemic proportions of obese people. Diabetes and chronic loss of sleep share the fact that both affect millions and one is detrimental to the other. Indeed, sleep deficits have marked modulatory effects on glucose metabolism and insulin sensitivity and foster metabolic syndrome that

l interactio... http://www.scielo.br/...

OSA and Diabetes

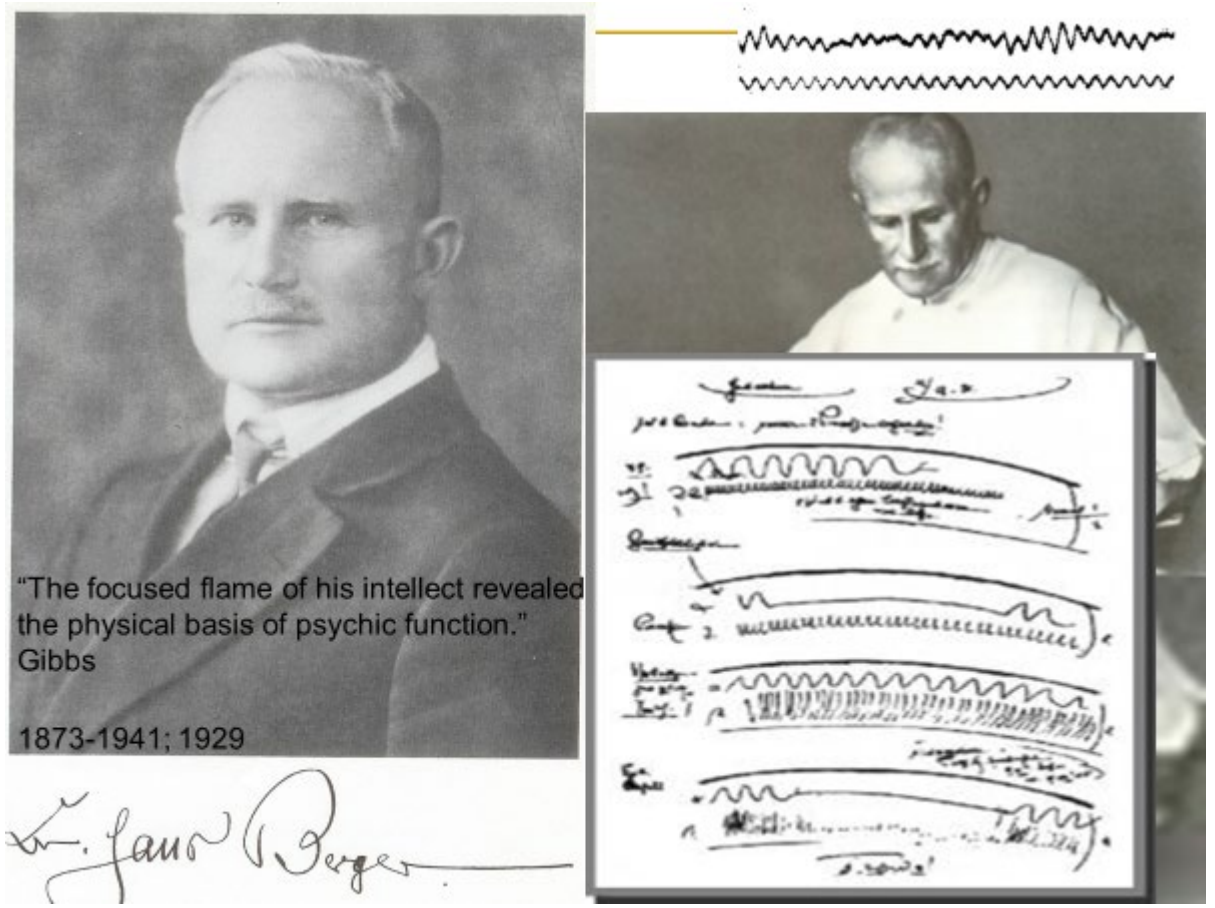
Kevin Hargrave, MD D.ABSM
CNS Clinic Lafayette
LASM 2009

(**sleep apnea**)…increasing AHI
was **associated with worsening insulin resistance independent of obesity**.

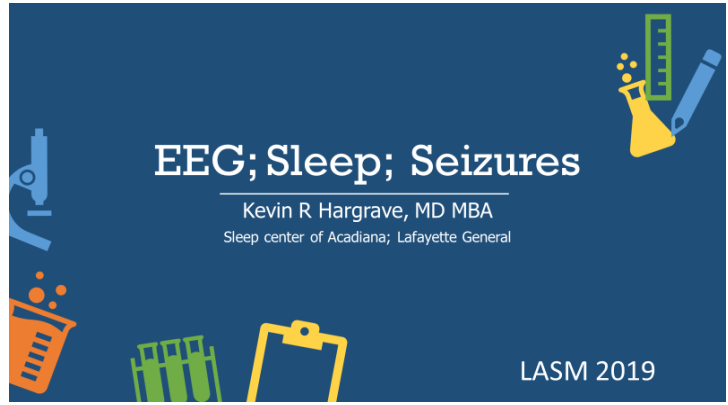
Sleep-disordered breathing and insulin resistance in middle-aged and overweight men.
Punjabi et al. Am J Respir Crit Care Med. 2002 Mar 1;165(5):677-82.

EEG

- Hans Berger 1929



Epilepsy/ Seizures



Differential Diagnosis of Nocturnal Events

	NREM Parasomnia	REM Behavior Disorder	Nocturnal Seizures	Psychogenic Events
Time of Occurrence	First 1/3 of night	During REM; latter 2/3 of night	Any time (most common during first 2 hours and last 2 hours of sleep)	Anytime
Memory of Event	Usually none	Dream recall	Usually none but frontal lobe may have some recall	None
Stereotypical Movements	No	No	Yes	No
PSG Findings	Arousal from delta sleep	XS EMG tone during REM sleep	Potentially epileptic activity	Occur from awake state

References

- Eisenschenk, Stephan UF Neurology
  com-neurology.sites.medinfo.ufl.edu/files/2012/02/EpilepsySleep.ppt

Cpap decreased seizure frequency by 45% Malow et al 2003

Epworth Sleepiness Scale

- No chance of dozing =0
- Slight chance of dozing =1
- Moderate chance of dozing =2
- High chance of dozing =3

Write down the number corresponding to your choice in the right hand column. Total your score below.

Situation	Chance of Dozing
Sitting and reading	•
Watching TV	•
Sitting inactive in a public place (e.g., a theater or a meeting)	•
As a passenger in a car for an hour without a break	•
Lying down to rest in the afternoon when circumstances permit	•
Sitting and talking to someone	•
Sitting quietly after a lunch without alcohol	•
In a car, while stopped for a few minutes in traffic	•

Total Score = _____

Analyze Your Score

Interpretation:

0-7: It is unlikely that you are abnormally sleepy.
8-9: You have an average amount of daytime sleepiness.
10-15: You may be excessively sleepy depending on the situation. You may want to consider seeking medical attention.
16-24: You are excessively sleepy and should consider seeking medical attention.

Reference: Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep* 1991; 14(6):540-5.

Eugeroic

- Wake promoting / new term?

Fibromyalgia

- sleep-related complaints are second only to pain

SLEEP 2017

Ghrelin

- Sleep restriction associated with increased Ghrelin levels (orexigenic; increases appetite) SLEEP p1311

Table 20-1

Origin and Main Action of Hormones

Hormone	Main Secreting Organ	Main Action in Adults
Growth hormone (GH)	Pituitary gland	Anabolic hormone that regulates body composition
Prolactin (PRL)	Pituitary gland	Stimulates lactation in women; pleiotropic actions
Adrenocorticotropic hormone (ACTH)	Pituitary gland	Stimulates release of cortisol from adrenal cortex
Cortisol	Adrenal cortex	Stress hormone, antiinsulin effects
Thyroid-stimulating hormone (TSH)	Pituitary gland	Stimulates the release of thyroid hormones from the thyroid gland
Luteinizing hormone (LH)	Pituitary gland	Stimulates ovarian and testicular function
Follicle-stimulating hormone (FSH)	Pituitary gland	Stimulates ovarian and testicular function
Testosterone	Gonads	Stimulates spermatogenesis
Estradiol	Ovaries	Stimulates follicular growth
Insulin	Pancreas	Regulates blood glucose levels
Melatonin	Pineal gland	Hormone of the dark that transmits information about the light-dark cycle
Leptin	Adipose tissue	Satiety hormone regulating energy balance
Ghrelin	Stomach	Hunger hormone regulating energy balance

SLEEP p202

Glaucoma

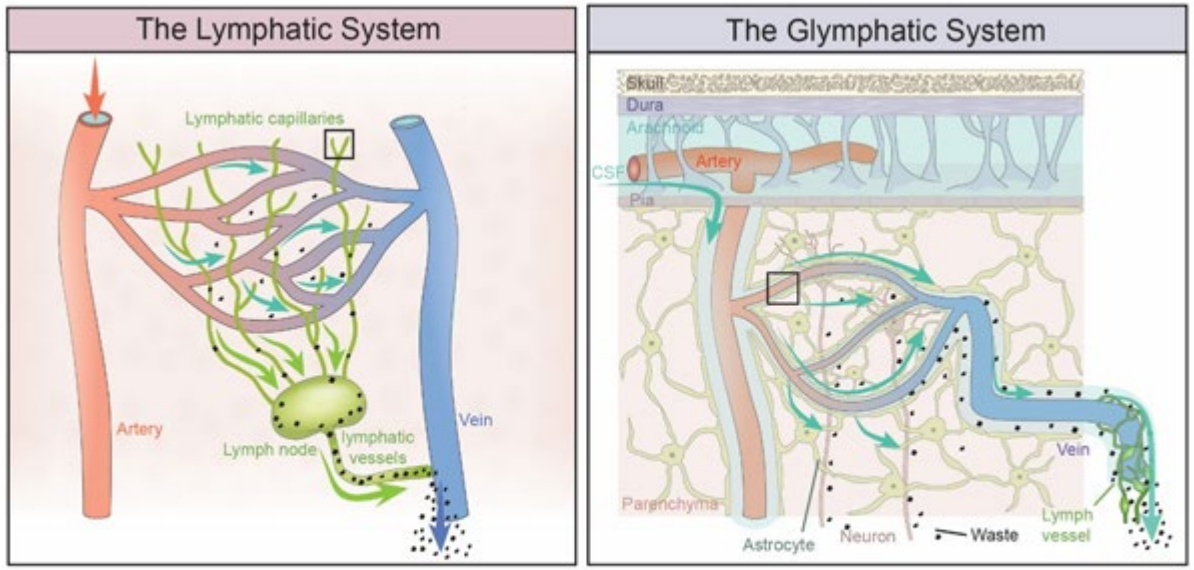
- OSA related to glaucoma

  Mcnab. the eye and sleep apnea sleep med rev 2007

Glymphatic system

Of interest, the glymphatic system is highly active during sleep and is disengaged mainly during wakefulness. This may contribute to the biological need for sleep that enables the elimination of potentially neurotoxic waste products. In an mouse model of AD, natural sleep or anesthesia was associated with a 60% increase in the interstitial space which correlated with increased convective exchange between the cerebrospinal fluid and interstitial fluid; this ultimately translated in an increased rate of β-amyloid clearance during sleep [6].

sciencedirect.com/topics/veterinary-science-and-veterinary-medicine/glymphatic-system



The lymphatic system in the periphery (left) and glymphatic system in the brain (right) are functionally homologous, enabling interstitial fluid movement, waste clearance, and immune surveillance of the tissue. Edited from: Hablitz and Nedergaard Current Biology 2021

urmc.rochester.edu/labs/hablitz/projects/glymphatic-lymphatic-homology.aspx

Sleep **Hygiene**

Peter Hauri PhD coined the term 1977

Hypothalamus

- Lesion anterior hypothalamus and intractable insomnia
- Lesion posterior hypothalamus and intractable hypersomnia

(1929 von Economo dorsal hypothalamus "sleepy sickness")

Insomnia

INSPIRE

CPAP intolerant
Ahi 15-65
BMI <35
DISE (Drug Induced Sleep Endoscopy)

inspiresleep.com

Inflammation

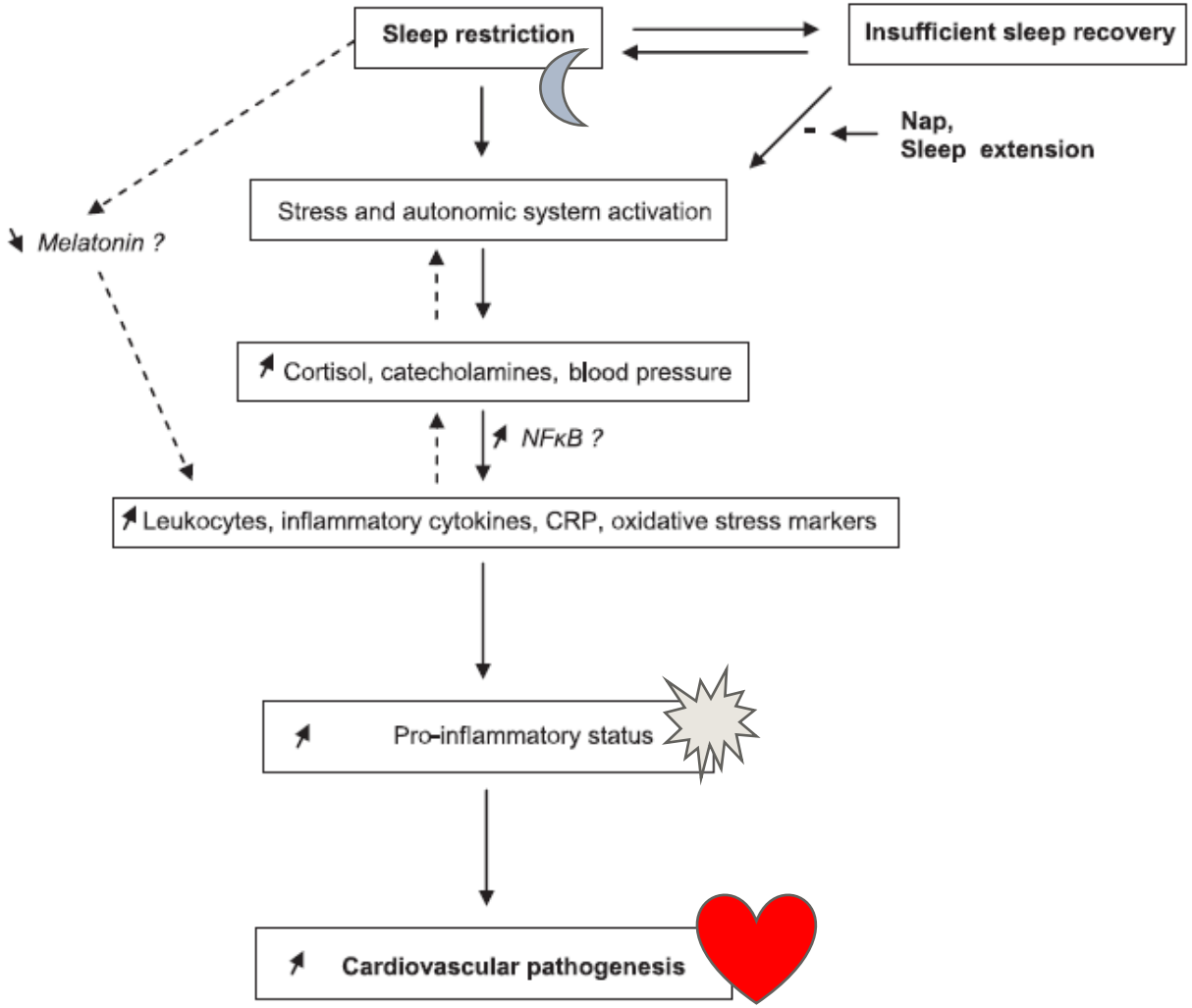


Fig. 1. Potential pathway(s) by which sleep restriction and insufficient recovery sleep lead to cardiovascular pathologies. Sleep restriction coupled to insufficient recovery sleep

Faraut et al 2012

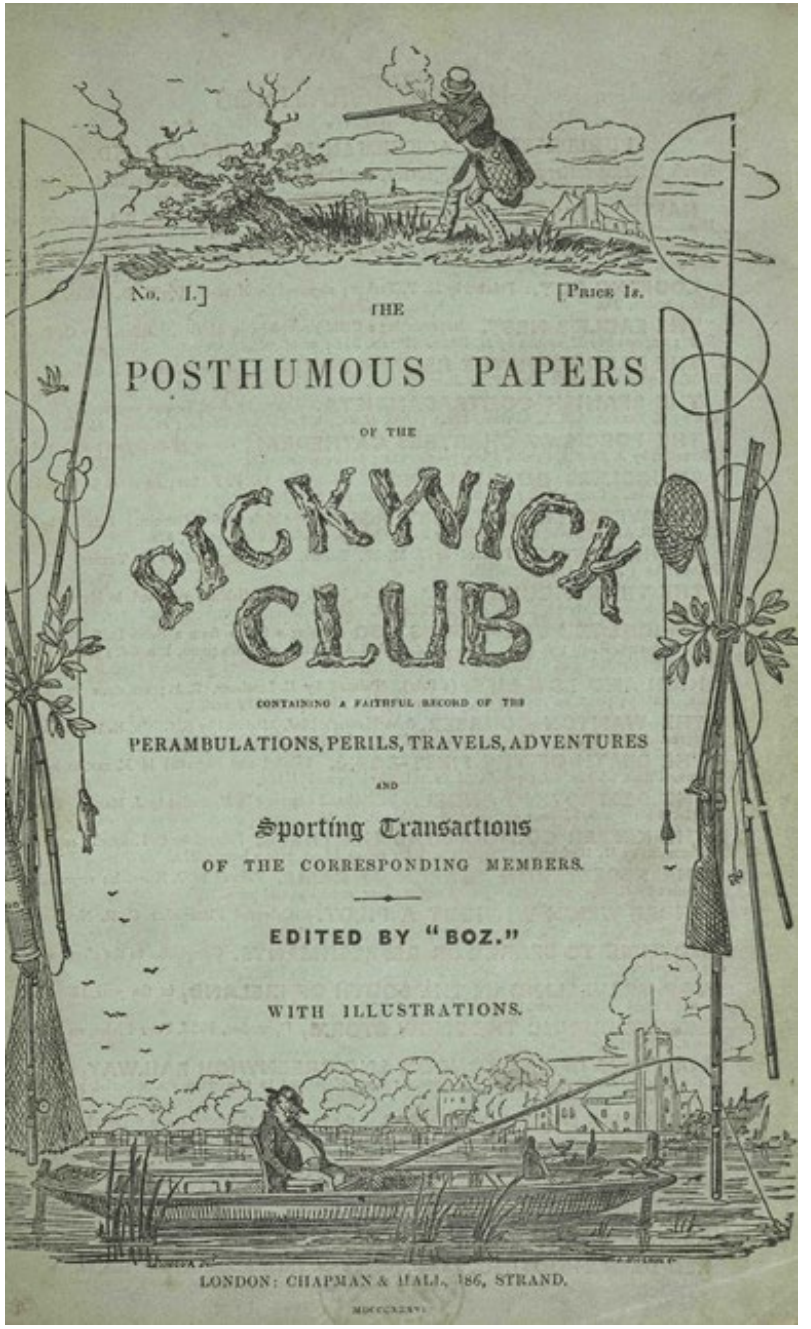
Joe

Charles Dickens

The posthumous papers of the Pickwick Club

Joe the fat boy

Obesity hypoventilation syndrome aka ‘Pickwickian’



Kleine - Levin syndrome

MacDonald Critchley in 1942 named condition KLS

1925 5 pt's Kleine Frankfurt

1935 more cases Levin NY

Hypersomnia accompanied by

- Adolescent onset (male predominate)
- Compulsive eating
- Hypersexuality
- Spontaneous resolution

Lark vs owl

Leptin

- Sleep deprivation assoc with decreased levels of leptin

SLEEP p1311

Table 20-1

Origin and Main Action of Hormones

Hormone	Main Secreting Organ	Main Action in Adults
Growth hormone (GH)	Pituitary gland	Anabolic hormone that regulates body composition
Prolactin (PRL)	Pituitary gland	Stimulates lactation in women; pleiotropic actions
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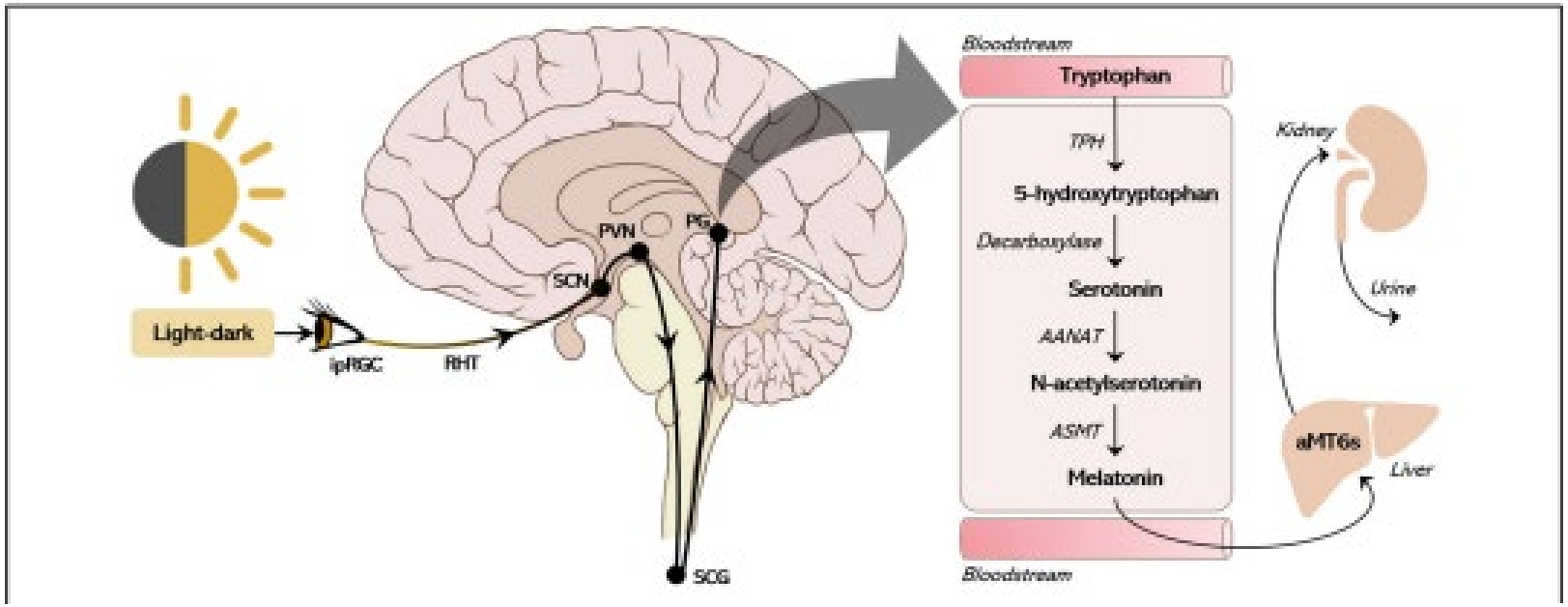
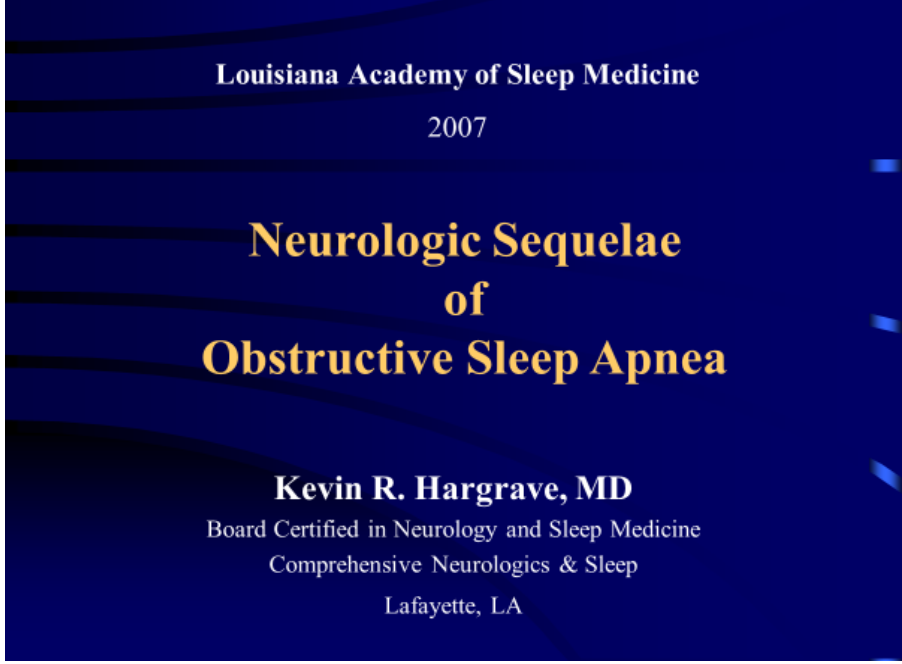
Testosterone	Gonads	Stimulates spermatogenesis
Estradiol	Ovaries	Stimulates follicular growth
Insulin	Pancreas	Regulates blood glucose levels
Melatonin	Pineal gland	Hormone of the dark that transmits information about the light-dark cycle
Leptin	Adipose tissue	Satiety hormone regulating energy balance
Ghrelin	Stomach	Hunger hormone regulating energy balance

SLEEP p202

Melatonin


Light-dark
ipRGC
RHT
SCN
PVN
PG
SCG
Bloodstream
Tryptophan
TPH
5-hydroxytryptophan
Decarboxylase
Serotonin
AANAT
N-acetylserotonin
ASMT
Melatonin
Bloodstream
Kidney
Urine
aMT6s
Liver

Migraine (HA) And Sleep



- HA's proximally related to sleep or upon awakening raise suspicion of sleep disorders
- OSA has been assoc with awakening HA patterns
- Night time fluctuations of O2 saturation with hypercapnia, vasodilation, and increased intracranial pressure

Provini Neurol Sci 2006

MS And Sleep

https://doi.org/10.5664/jcsm.10304

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Sleep in multiple sclerosis: a systematic review and meta-analysis of polysomnographic findings

Ye Zhang, MD, PhD[1]; Rong Ren, MD, PhD[1]; Linghui Yang, BA[1]; Haipeng Zhang, MD[1]; Yuan Shi, MD[1]; Michael V. Vitiello, PhD[2]; Larry D. Sanford, PhD[3]; Xiangdong Tang, MD, PhD[1]

[1]Sleep Medicine Center, Department of Respiratory and Critical Care Medicine, Mental Health Center, Translational Neuroscience Center, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China; [2]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington; [3]Sleep Research Laboratory, Center for Integrative Neuroscience and Inflammatory Diseases, Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, Virginia

Study Objectives: This study aims to explore the polysomnographically measured sleep differences between patients with multiple sclerosis (MS) and healthy control patients.

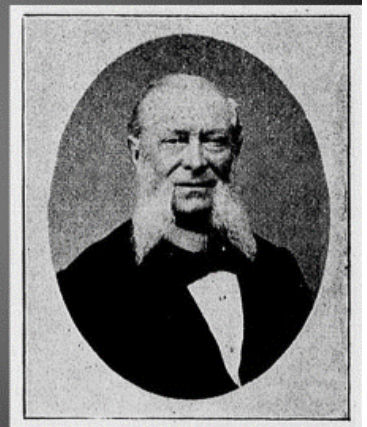
- patients with MS have objectively decreased sleep quantity and quality.
- These changes are important because decreased sleep amount and increased sleep fragmentation may exacerbate alterations in autoimmune processes.

Narcolepsie

Gelineau, E.
de la Narcolepsie. Gaz Hop Paris55:623. 1880

"rare, little known neurosis characterized by an imperative need to sleep of sudden onset and short duration, recurring at more or less close intervals."
Narcos (somnolence) lepsie (seize)

Dr. Jean Baptiste Edouard Gélineau (1828–1906)

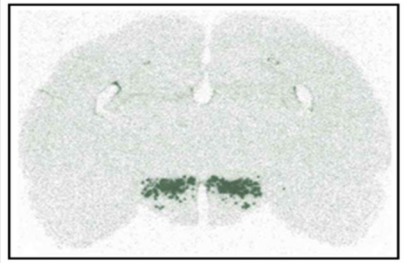


D' JEAN-BAPTISTE-ÉDOUARD GÉLINEAU

Karl Friedrich Otto Westphal (1833-1890)

Westphal clearly grasped that the cataplectic attacks involved loss of muscle tone without associated loss of consciousness, and his comment about sleeplessness may have indicated the presence of disrupted nocturnal sleep that is common in narcolepsy. 1877 pub

Loewenfeld described cataplexy in 1902 then Henneberg coined the term from a greek word in 1916



The first image of the hypocretin system. This autoradiograph shows the result of an in situ hybridization experiment showing the expression of hypocretins in a coronal section from rat brain. A few thousand neurons express Hcrts in the lateral hypothalamus http://delecea.stanford.edu/research.html

Humans:70,000 Hcrt cells

1. somnolence, paralysis of cranial nerves, extremities and eye muscles and expressionless faces.,often leading to coma and death.

2. hyperkinetic form manifested itself with restlessness, motor disturbances as twitching of muscle groups, involuntary movements, anxious mental state and insomnia or inversion of sleep patterns.

3. postencephalitic parkinsonism. The symptoms were weakness of muscles, rigidity of movements and insomnia or sleep inversion.

Von Economo published his findings in an article of 1917, "Die Encephalitis lethargica," He was inspired by this illness to search for a centre of sleep in the brain.

Constantin Freiherr von Economo (1876 – 1931)

Epidemiology

- >85% N/C or N type 1 or Hcrt deficiency have HLA DQB1*0602
  - 87% in sporadic cases; 70% in familial cases
- H1N1 vacc & strep infections may be immunological triggers
- N wo cataplexy 10-50% of cases of 'narcolepsy' aka N type 2

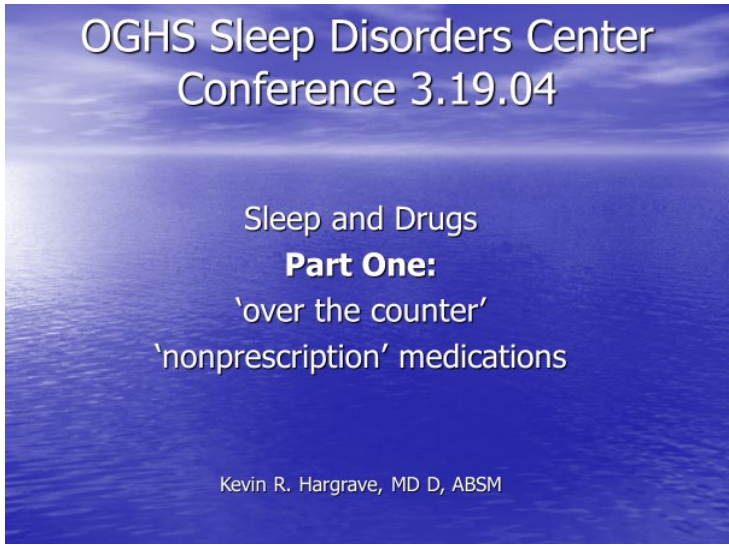
Neuropathy

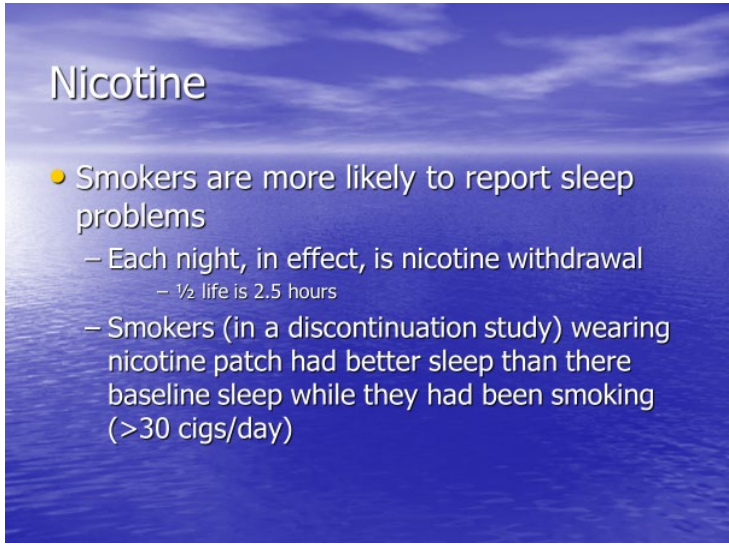
- In diabetics with autonomic neuropathy ¼ has OSA

Nicotine

- Nicotinic AchR's
- Elimination half life 2.5 h
- Transdermal nicotine increases wake and decreases REM
- Withdrawal disrupts sleep
- Nicotine patches may cause nightmares
- Does not help OSA but keeps obese nonsmoker OSA pt's awake

Davilla et al AJCCRM 94





Night Terrors

- Prepubertal age 5-7 typical
- Only 1% or fewer adults

- Deep sleep or N3 early in the night
- Piercing scream
- Intense fear

The Nobel Prize in Physiology or Medicine 2017

© Nobel Media. Ill. N. Elmehed

Jeffrey C. Hall

Prize share: 1/3

© Nobel Media. Ill. N. Elmehed

Michael Rosbash

Prize share: 1/3

© Nobel Media. Ill. N. Elmehed

Michael W. Young

Prize share: 1/3

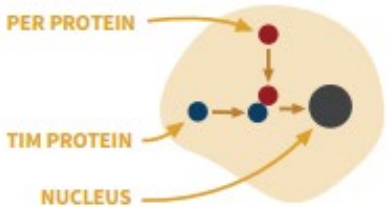
2017 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

The Nobel Prize in Physiology or Medicine 2017 was awarded to Jeffrey C. Hall, Michael Rosbash, and Michael W. Young for discovering the molecular mechanisms behind circadian rhythms.

Living organisms have an internal biological clock, known as a circadian rhythm, which adapts our physiology to different times of the day. Behaviour, body temperature, hormone levels, sleep, and metabolism are all affected by our circadian rhythm.

PER PROTEIN

A gene called the 'period' gene is involved in circadian rhythms. It produces a protein called PER. This protein builds up during the night and breaks down during the day.



PER builds up in cell nuclei. It binds to a protein called TIM, produced by the 'timeless' gene, so they can both enter the nucleus where genetic material is located.

In the nucleus PER blocks period gene activity, stopping its own synthesis. The 'doubletime' gene codes for the DBT protein that delays PER build-up, adjusting it to a 24 hour cycle.

WHY DOES THIS RESEARCH MATTER?

Our internal clock is involved in many of our body's functions. By understanding its molecular basis, we can better understand what happens when it is disrupted, for example in the case of jet lag. It may also help in understanding disease risk and treatment.

Nobel Prize in Medicine or Physiology Press release: https://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/press.html

COMPOUND iNTEREST

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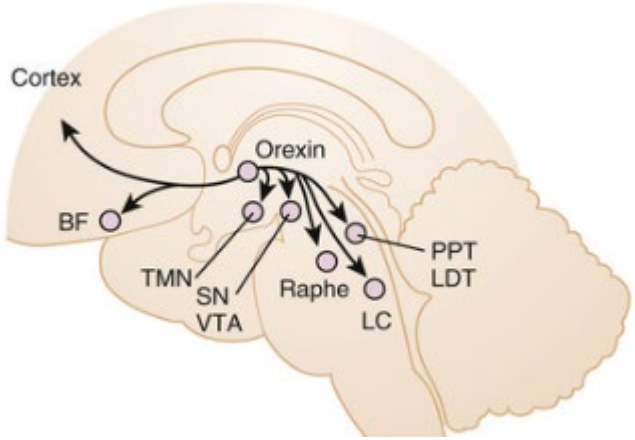
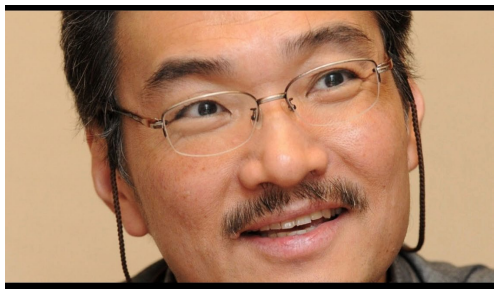
Orexin / (Hypocretin)

- Orexis Gr: appetite
- Elucidated 1998
- Normal csf >200 pg/ml
- Low <110
- Low in narcolepsy type 1
- PD pt's w DA related sedation may have partial hypocretin defic

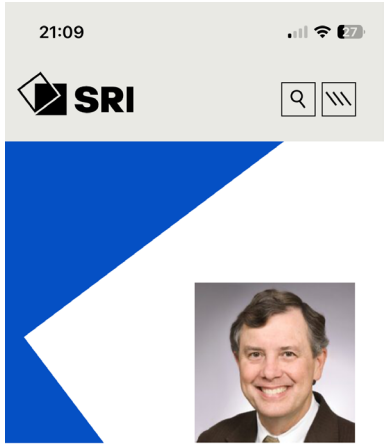




Masashi Yanagisawa

Japanese molecular biologist

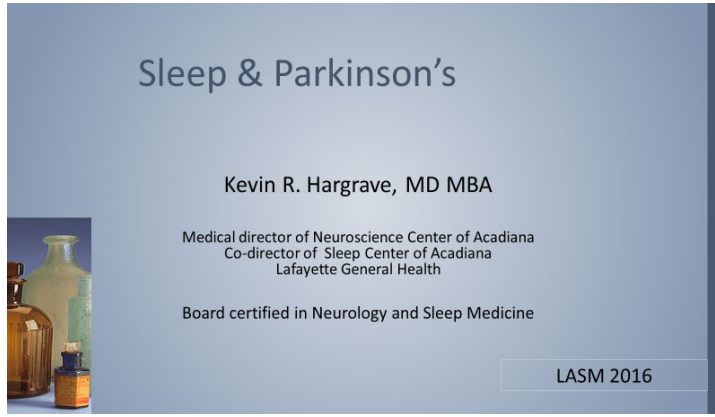
Masashi Yanagisawa (柳沢 正史, *Yanagisawa Masashi*, born May 25, 1960) is a Japanese-American molecular biologist and physician, famous for his discovery of the hormone endothelin and the neuropeptide orexin, the absence of which is the cause of narcolepsy. He is currently the



Thomas Kilduff
Center Director, Center for Neuroscience

Thomas Kilduff, Ph.D., is an expert in the neurobiology of sleep and wakefulness.

Parkinson's



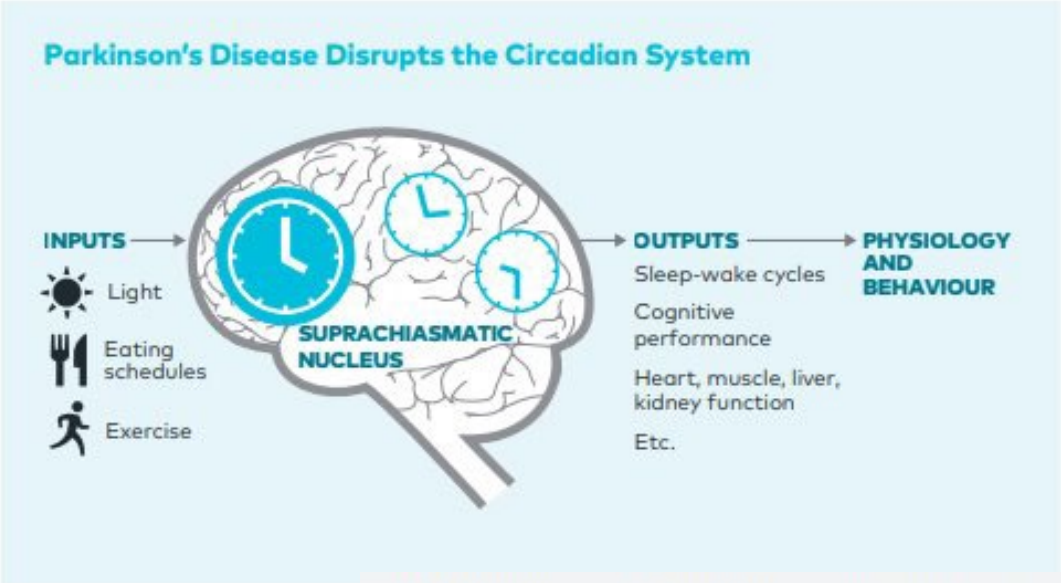
PD pt's have increased prevalence of

- insomnia,
- disrupted sleep,
- or other sleep problems (>60%)

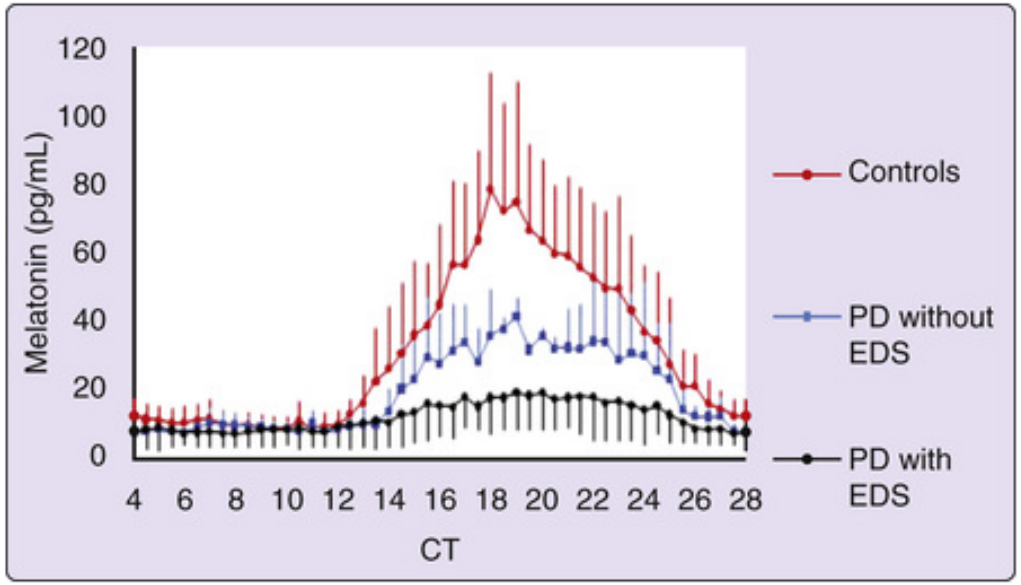
Can have daytime sleep attacks made worse by dopamine agonists

1/3 at least 1 RBD episode per week

Parkinson's



parkinson.org/sites/default/files/documents/sleep.pdf



SLEEP Kryger et al

Medicine®

OBSERVATIONAL STUDY

OPEN

Increased Risk of Parkinson's Disease in Patients With Obstructive Sleep Apnea

A Population-Based, Propensity Score-Matched, Longitudinal Follow-Up Study

Nai-Cheng Yeh, MD, Kai-Jen Tien, MD, Chun-Ming Yang, MD, Jhi-Joung Wang, MD, and Shih-Feng Weng, PhD

Abstract: Obstructive sleep apnea (OSA), characterized by repetitive episodes of apnea/hypopnea and hypoxia, is associated with systemic inflammation and induces metabolic, endocrine, and cardiovascular diseases. Inflammation might have an impact on neurodegenerative diseases. This study investigates the possible association between OSA and Parkinson's disease (PD). Random samples out of 1 million individuals were collected from Taiwan's National Health Insurance

kidney disease had a higher risk for PD than their counter parts. Log-rank analysis revealed that patients with OSA had significantly higher cumulative incidence rates of PD than the comparison group ($P = 0.0048$). Patients with OSA are at an increased risk for subsequent PD, especially elderly male patients.

(*Medicine* 95(2):e2293)

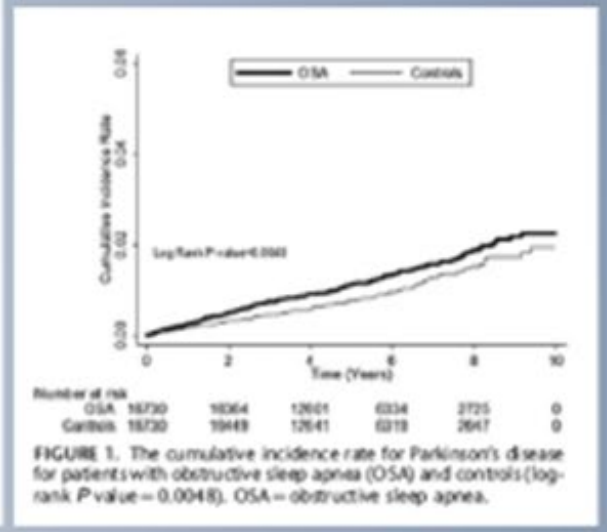


FIGURE 1. The cumulative incidence rate for Parkinson's disease for patients with obstructive sleep apnea (OSA) and controls (log-rank P value = 0.0048). OSA = obstructive sleep apnea.

DBS and sleep in PD

deep brain stimulation (DBS) has been shown

to improve sleep in PD

2002; Monaca et al., 2004). Subthalamic nucleus (STN) DBS has been shown to increase total sleep time, decrease wakefulness after sleep onset, and increase time spent in non-rapid eye movement (NREM) stage 2 (N2) sleep (**Arnulf et al., 2000**; **Monaca et al., 2004**). Still, results are mixed, with other studies showing a trend towards a decrease in N2 sleep (though not reaching statistical significance; Iranzo et al., 2002), or no change in N2 sleep but an increase in NREM stage 3 (N3; Monaca et al., 2004).

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Parkinsonian Daytime Sleep-Wake Classification using Deep Brain Stimulation Lead Recordings

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[1]Department of Neurology, University of Minnesota, Minneapolis

Highlights

- Daytime sleepiness occurs in Parkinson's disease (PD), but treatment options remain lacking.
- DBS is an effective treatment option for PD motor signs.
- Daytime sleep-wake states can be classified based on DBS lead recordings with >85% accuracy.
- Results can guide closed-loop DBS systems for mitigating daytime sleepiness in PD.

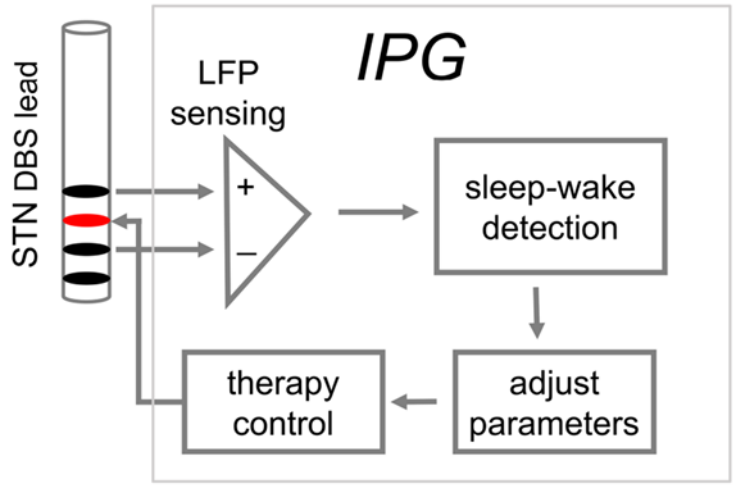


Figure 1.
An example of a closed-loop DBS paradigm for automatic detection and disruption of sleep-related neural oscillations. A major first step towards the realization of this paradigm will be a reliable identification of daytime sleep-wake states using DBS lead sensing. This manuscript examines the plausibility of classifying daytime sleep-wake states using DBS lead recorded STN local field potentials.

Periodic Limb Movement d.o. (PLMD)

- Pathophysiologically same as RLS but after sleep onset
- SSRI's worsen just as they do RLS

Restless Legs Syndrome (RLS)

Urge to move the legs
At rest or inactivity; worse at night
Relieved partially at least by mvmt

serum and csf ferritin (Earley 2005)
low brain iron stores by MRI and autopsy (Allen 2001, Connor 2003)

Treat if ferritin <45

PDE inhibitors (ED tx)

Avoidance of Alcoholic Beverages, Benzodiazepines, and Phosphodiesterase-5 Inhibitors at Bedtime, and Smoking

The use of alcoholic beverages and benzodiazepines may increase the likelihood of upper airway occlusion by promoting the relaxation of the muscles of the upper airway. We also advise patients that phosphodiesterase inhibitors used to treat erectile dysfunction (e.g., sildenafil [Viagra], vardenafil [Levitra], and tadalafil [Cialis]) may worsen OSA. In a randomized double-blind placebo-controlled study, [100] it was shown that 50 mg of sildenafil significantly increased the obstructive AHI and desaturation in a group of patients with OSA.

Roizenblatt Arch Int Med 2006

Quviviq

Orexin antagonists

	FDA approv
• suvorexant (Belsomra) Merck	2014
• lemborexant (Dayvigo) Eisai	2019
• daridorexant (Quviviq) Idorsia	2022

REM behavior d.o. (RBD)

- MSA 90%
- DLB 80%
- PD 60%
- PSP 10%
- HD 8%

Bed partner safety

Melatonin; Clonazepam

Antidepressants may cause or worsen or could be helpful

Male to female 9:1

Shift work

- Shift workers at increased risk of metabolic syndrome
- Shift workers may be at increased risk of cancer

Stroke; cerebral infarct (CVA)

Modifiable Risk Factors:

Hypertension
Diabetes
Dyslipidemia
Carotid stenosis

Atrial fibrillation
CHF
Hypercoagulability

Smoking

Endothelial dysfunction

OSA

OSA is an independent [illegible]
TIA or stroke patients [illegible]
[illegible]
[illegible]

Slide from LASM 2004
OSA and Stroke

Obstructive Sleep Apnea (OSA)	**Stroke; cerebral infarct (CVA)**
exacerbates:	Modifiable Risk Factors:
Hypertension( )	Hypertension
Diabetes ( )	Diabetes
Dyslipidemia ( )	Dyslipidemia
Carotid stenosis ( )	Carotid stenosis
Atrial fibrillation ( )	Atrial fibrillation
CHF( )	CHF
Hypercoagulability	Hypercoagulability
*Smoking	Smoking
Endothelial dysfunction()	Endothelial dysfunction

OSA

OSA is an independent risk factor for stroke

TIA or stroke patients should be screened for OSA

Conversely, stroke can cause or exacerbate OSA

Treating OSA can prevent further strokes or other vascular events

OSA and TIA/stroke awareness

- Mean latency of stroke / TIA and dx of OSA was >4y

Shulz et al Pneumologie 2000

Could be better now? [the above from my 2003 stroke osa talk]

Frequency of Sleep Apnea in Stroke and TIA Patients: A Meta-analysis

Karin G. Johnson, M.D.[1]; Douglas C. Johnson, M.D.[2]

[1]Baystate Medical Center, Springfield, MA; [2]Massachusetts General Hospital, Boston, MA

Study Objectives: To determine the frequency of sleep disordered breathing (SDB) in ischemic and hemorrhagic stroke and transient ischemic attack (TIA) patients by meta-analysis.

Methods: A systematic literature search using Medline, EMBASE and CINAHL and a manual review of references through December 2008 was conducted using specific search terms. The frequency of SDB stratified by apnea hypopnea index (AHI) was extracted by the author. Weighted averages using a random-effects model are reported with 95% confidence intervals.

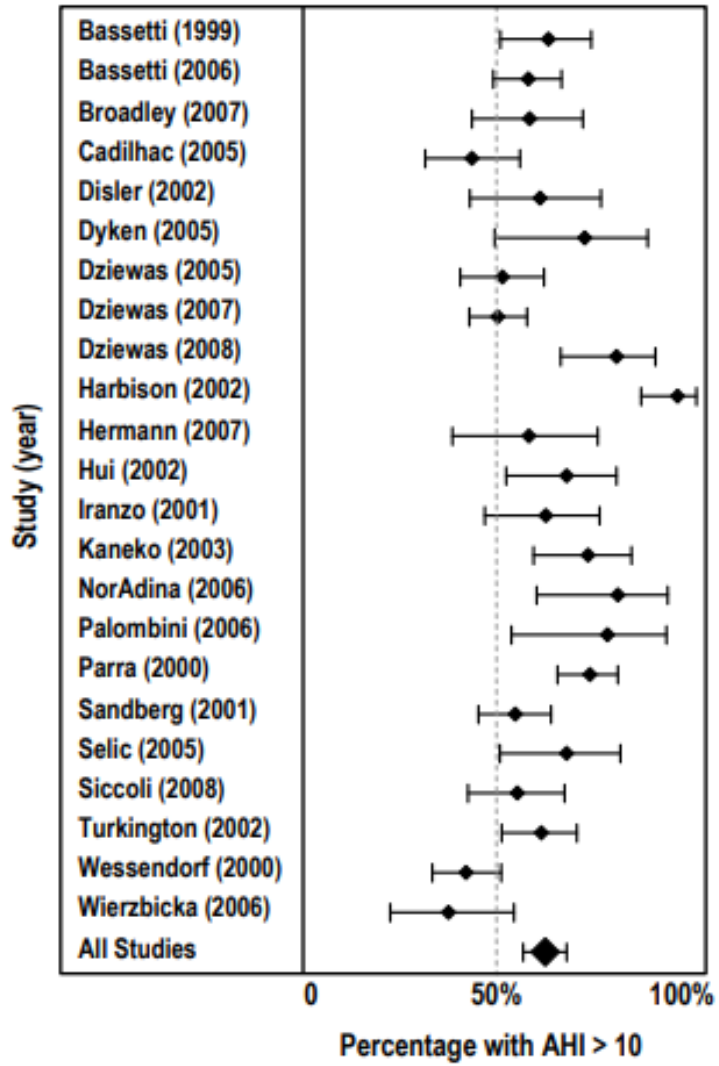
Results: Twenty-nine articles evaluating patients with auto-CPAP, limited-channel sleep study, or full polysomnography were included in this study. In meta-analysis of 2,343 ischemic or hemorrhagic stroke and TIA patients, the frequency of SDB with AHI > 5 was 72% and with AHI > 20 was 38%. Only 7% of the SDB was primarily central apnea. There was no significant difference in SDB prevalence by event type, timing after stroke, or type of monitoring. Males had a higher percentage of SDB (AHI > 10) than females (65% compared to 48% p = 0.001). Patients with recurrent strokes had a higher percentage of SDB (AHI > 10) than initial strokes (74% compared to 57% p = 0.013). Patients with unknown etiology of stroke had a higher and cardioembolic etiology a lower percentage of SDB than other etiologies.

Conclusions: SDB is very common in stroke patients irrespective of type of stroke or timing after stroke and is typically obstructive in nature. Since clinical history alone does not identify many patients with SDB, sleep studies should be considered in all stroke and TIA patients.

Keywords: Stroke prevention, all cerebrovascular disease/strok, sleep apne, prevalence studies, screening in epidemiology

Citation: Johnson KG; Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. *J Clin Sleep Med* 2010;6(2):131-137.

Figure 1—Forest plot of percentage of patients with AHI > 10 with 95% confidence intervals.



T, U, V, W, X, Y

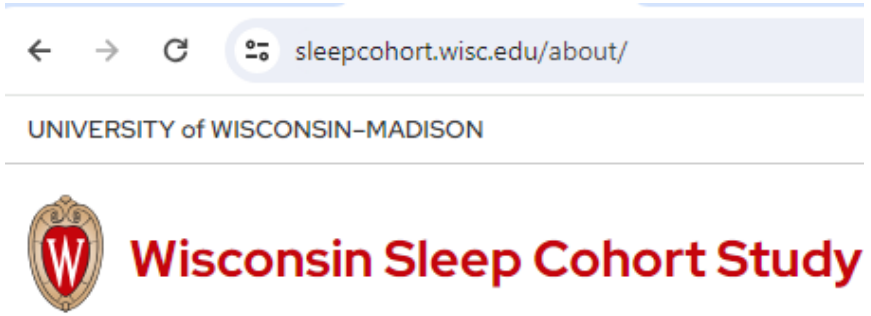
Telomere shortening associated with poor quality sleep

SLEEP p37

Uvula; Uvulopharyngoplasty (UPPP)
Upper airway resistance syndrome (UARS)

Valerian (valeriana officinalis)

Wisconsin sleep cohort study(ies)
709pt PSG's, after 4yr OR HTN 3 if AHI >15



eXercise

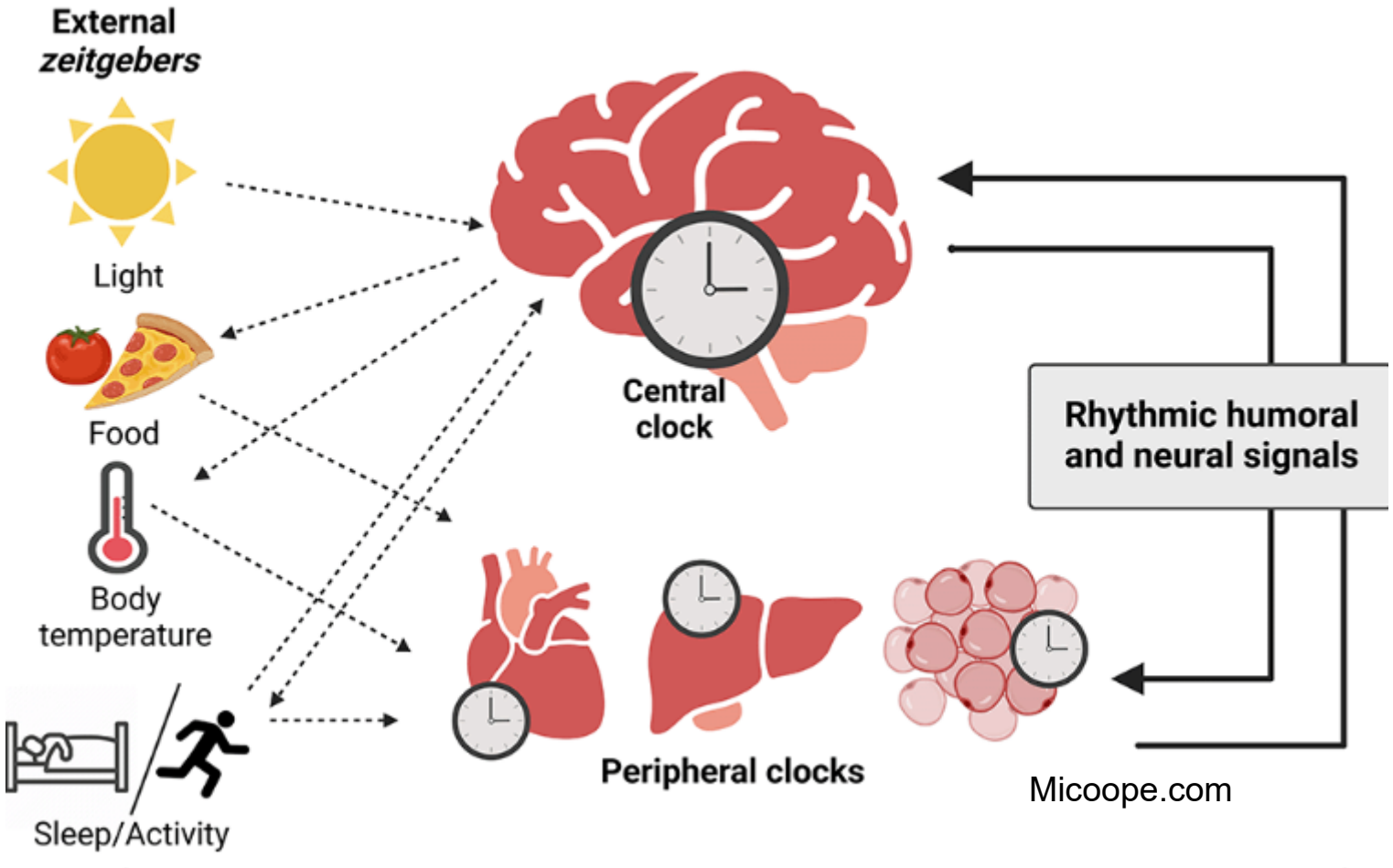
Youth

Z drugs

- zopiclone first z drug approved Europe 1986
  - Eszopiclone approved US 2004
- zolpidem (Ambien) approved US 1992

Zeitgeibers

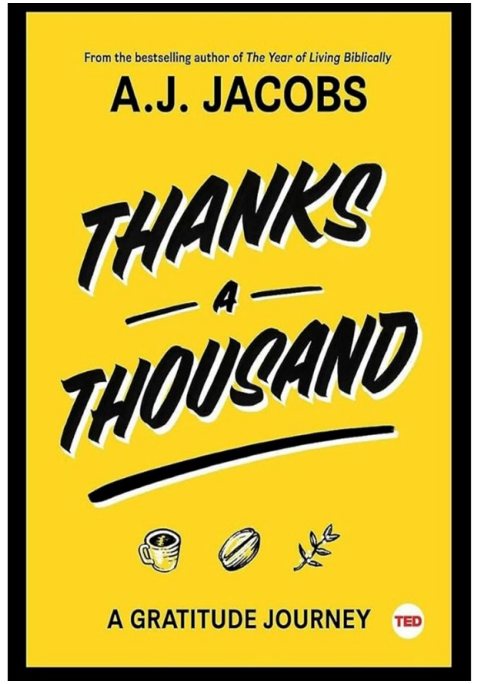
‘time givers’ or ‘time cues’



WORD OF THE DAY
MAY 11, 2024
zhuzh
verb | ZHUZH (the U is as in PUSH)
What It Means
To zhuzh something up is to improve its flavor or appearance by way of a small improvement, adjustment, or addition.
// He likes to zhuzh up his outfits with brightly-colored ties.

OSA

A	Age, alcohol, Alzheimer's ds
B	Bruxism
C	Caffeine/adenosine, Cancer, Carpal tunnel syndrome, circadian, Cluster HA, CPAP
D	Diabetes
E	EEG, Epilepsy, Epworth Sleepiness Scale; eugeroic
F	fibromyalgia
G	ghrelin
H	sleep Hygiene, hypothalamus
I	insomnia, INSPIRE, inflammation
J	Joe (the fat boy from Pickwick papers)
K	Kleine Levin syndrome
L	lark vs owl; Leptin
M	migraine; MS
N	narcolepsy; nicotine; night terrors; 2017 Nobel prize
O	orexin; OSA;
P	Parkinson's 'PD'; PLMD; PDEi
Q	Quviviq etc
R	REM Behavior d.o. 'RBD'; RLS
S	shift work; stroke
T	telomeres
U	uvula; UPPP; UARS
V	valerian
W	Wisconsin sleep cohort study
X	eXercise
Y	youth
Z	z drugs; zeitgebers; zhuzh



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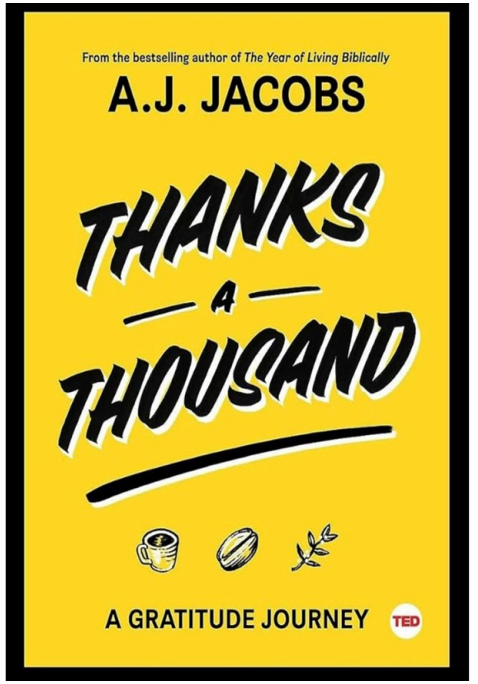

Thanks

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