### **SLEEP AND COGNITION**

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# **Sleep and Cognition**

#### Goals for today:

- 1.Understand the physiology of memory and learning, and how sleep can affect this
- 2. Understand the prevalence of sleep disorders in dementia
- 3.Learn how sleep disorders can affect memory
- 4. Increase awareness of how neurologic disorders associated with cognitive problems can result in sleep disorders
- 5.Be able to discuss the effects of medications to treat insomnia on cognition
- 6. Understand the impact of sleep disorders on children and learning

# **Physiology of Memory**

How are memories made?

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- Memory is the capability of the brain to encode, store, and retrieve information.
- Structures of the brain associated with memory function include the hippocampus, parahippocampal gyrus, fornix, mammillary bodies and cingulate gyrus.
- To form new memories, information needs to be changed to usable data, through a process called *encoding*. Once encoded, memory is stored for later use.
  - Much of what is stored lies outside of our awareness, except when we need it.
  - Retrieval of memories bring stored memories into consciousness.

# **Types of Memory**

- Sensory memory
- Short-term memory
- Long-term memory



## **Sensory Memory**

#### Sensory Memory

- Shortest form of memory
- Is the capacity to store impressions
- We receive stimulus from the 5 senses, which are stored briefly but accurately
- Storage of this type of memory is done automatically
- Sensory memory translates into short term memory through the process of *attention* which is selectively concentrating on one aspect of the environment, while ignoring other factors

# Short Term Memory (STM)

- Defined as the maintenance of information over a brief period of time (generally 15 seconds to 1 minute)
- Results from conscious maintenance of sensory stimuli within that time period
- Short term memory is also known as "working memory"
- Involves remembering and processing information at the same time
- Short term memory becomes long term memory when information is stored through a process called *consolidation*
- Consolidation of memory is enhanced through repetition, which associates new information with previous knowledge and/or a subject of interest
- The prefrontal cortex is the primary area of the brain responsible for short term memory

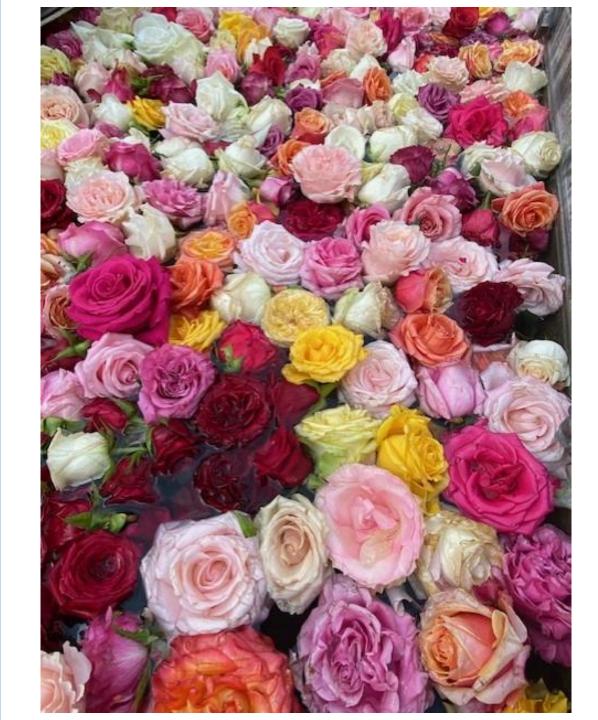
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# Long Term Memory

- Refers to the continuing storage of information
- Information is largely outside of our awareness but can be recalled into working memory and used when needed
- As opposed to short term memory, information in long term memory can last between months and decades
- Long term memory is divided into two types:
  - <u>Explicit memory</u> (declarative memory)-all memories available in consciousness
    - Is further divided into:
      - Episodic memory (related to specific events)
      - Semantic memory (related to knowledge about the world)
  - Implicit memory

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- Mostly unconscious
- Includes <u>procedural memory</u> (memory of body movement, how to use tools/objects in environment, like driving a car)



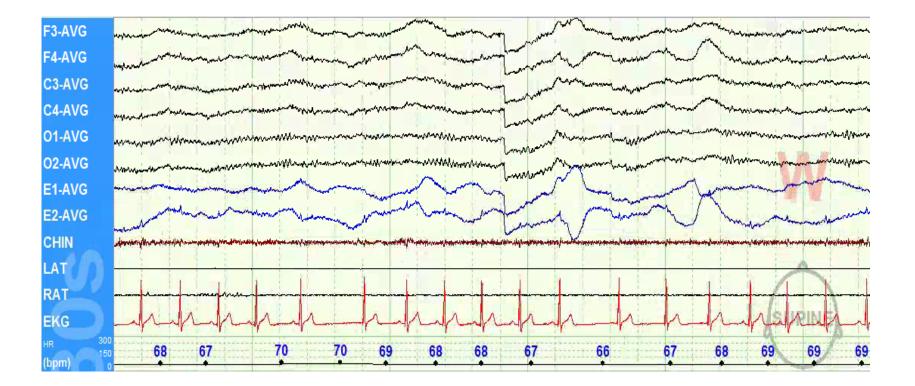
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# **Sleep Stages by EEG**

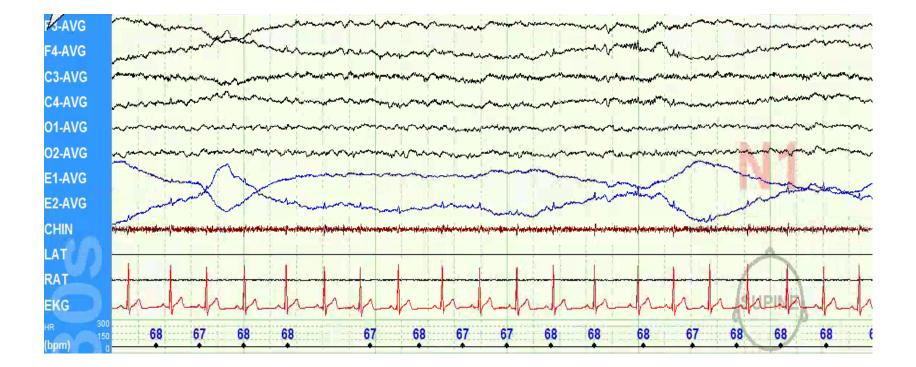
Wake

- N1 (stage 1)-Non-Rapid Eye Movement (NREM)
- N2 (stage 2)-Non-Rapid Eye Movement (NREM)
- N3 (stage slow wave, used to be stages 3 and 4)-Non-REM (NREM)
- R (stage REM)-Rapid eye movement sleep

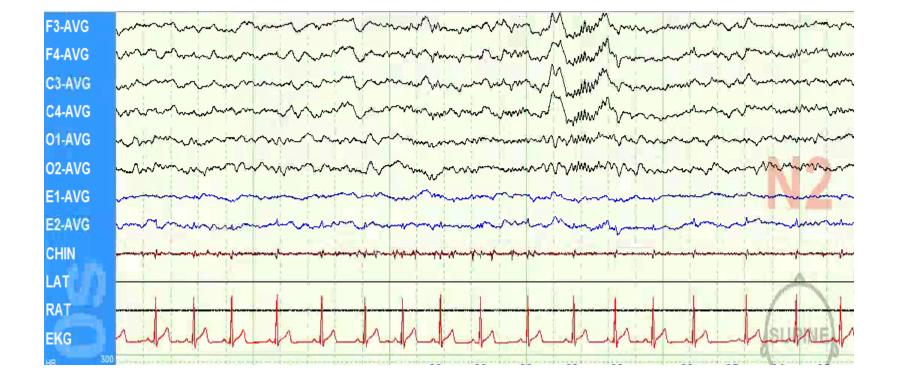
# Stage Wake



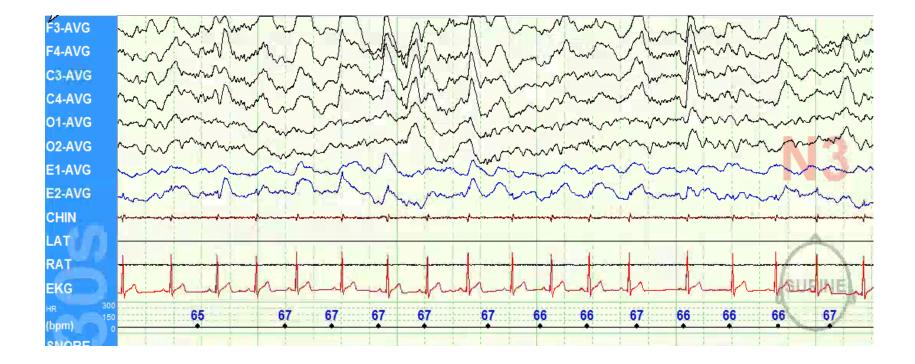
# Stage 1 Sleep (N1 Sleep)



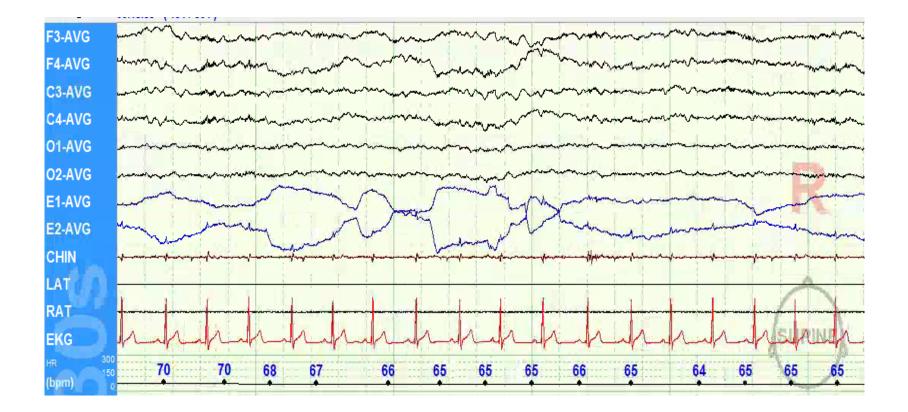
# Stage 2 Sleep (N2 Sleep)



# Stage Slow Wave (N3) Sleep



# **REM Sleep**



### **How Does Sleep Affect Memory?**

- Memory consolidation, the process of converting short term memory into long term memory, with preserving important memories and eliminating extraneous information, takes place via non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM).
  - During NREM sleep the brain sorts out important memories and eliminates other information. Deep sleep in NREM helps to solidify memory
  - In REM, memories are further processed, particularly emotional memories
- Recent studies have shown that both insufficient sleep and excessive sleep can affect memory processing.
- Need to get enough sleep to process new information, sleep prepares the brain to learn new information the next day.
- Sleeping after learning consolidates new information into memories.
- Inadequate sleep can lower the ability to learn by as much as 40%.

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## Sleep, Memory and Aging

- Sleep quality decreases with age.
- Aging is associated with reduced slow wave sleep (brain waves produced in the medial prefrontal cortex).
- As a person ages, the prefrontal cortex deteriorates, thus resulting in a reduced amount of slow wave sleep.
- The less slow wave sleep, the harder it is to process memories.
- The brain has a relatively newly discovered lymphatic like system (the glymphatic system) that is a series of channels in the brain formed by astroglial cells that provide elimination of soluble proteins and metabolites from the central nervous system.
- Slow wave sleep may be essential for the brain's glymphatic system to flush out abnormal proteins like beta amyloid in order to cleanse the brain of proteins that can be associated with Alzheimer's disease.

### Pathology of Alzheimer's Disease A Brief Review

- Alzheimer's disease begins when plaques of the protein amyloid beta start building up in the brain.
- After years of amyloid accumulation, a second brain protein, tau, begins to form tangles that are toxic to neurons.
- Cognitive problems start to occur when tau tangles become detectable.



### Deep Sleep Might Help Against Memory Loss

Research article Open Access Published: 03 May 2023

### NREM sleep as a novel protective cognitive reserve factor in the face of Alzheimer's disease pathology

Zsófia Zavecz <sup>CD</sup>, <u>Vyoma D. Shah</u>, <u>Olivia G. Murillo</u>, <u>Raphael Vallat</u>, <u>Bryce A. Mander</u>, <u>Joseph R. Winer</u>, <u>William J. Jagust & Matthew P. Walker</u> <sup>CD</sup>

<u>BMC Medicine</u> **21**, Article number: 156 (2023) Cite this article **1067** Accesses **324** Altmetric Metrics

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### Slow Wave Sleep as a "Cognitive Reserve Factor"

- Slow wave sleep may increase resilience against beta-amyloid protein in the brain that is associated with memory loss caused by dementia.
- Researchers at UC Berkley have shown that superior amounts of slow wave sleep can act as a protective factor against memory decline in people who already have a high burden of Alzheimer's disease pathology.
- People can have an increased amount of Alzheimer's disease pathology in their brain but not necessarily be destined to have cognitive problems or memory loss (certain lifestyle factors can moderate and decrease risk).
- Previously, the researchers found that reduced amount of slow wave sleep may forecast a faster rate of beta amyloid accumulation in the brain, with the resultant conversion to dementia being more likely.

### **Concept of Cognitive Reserve Factors**

- Physical activity, social interaction, years of education are considered "cognitive reserve factors" that are believed to provide resilience to severe brain pathology in dementia. The researchers wondered if sleep could also factor in to provide resilience.
- They recruited 62 non-demented older adults to sleep with EEG analysis and undergo PET scanning to measure beta amyloid deposition in the brain.
- Half of the participants had high burden of beta amyloid and half did not.
- After they slept, they had a memory test with matching names to faces.
- Those with high amounts of beta amyloid who also got higher levels of deep sleep performed better on the memory test than those with the same amount of beta amyloid but who had less slow wave sleep. This difference was seen only in the group with the high beta amyloid.

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 This effect was not seen in the group without beta amyloid pathology. Deep sleep had no additional supportive effect on memory-as they felt that there was no demand for resilience factors in otherwise intact cognition.

### Slow Wave Sleep and Cognitive Reserve Factors-Conclusion

- Sleep, independent of other cognitive reserve factors (education and physical activity), contributes to salvaging memory functioning in the face of brain pathology.
- This information illustrates the importance of slow wave sleep in counteracting the memory impairing effects of beta amyloid deposition.

## **Sleep Disorders and Memory**

- Adequate sleep is essential for formation and consolidation of memories
- Anything that disturbs sleep or prevents sleep can result in cognitive impairment, including reduced memory function.
  - Shift work
  - Insufficient sleep-volitional
  - Insomnia-disorders of initiating and maintaining sleep with excessive daytime sleepiness.
  - Disorders of excessive daytime sleepiness-for example,
    - Obstructive sleep apnea
    - Narcolepsy



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## **Dementia and Sleep Disorders**

- In a multicenter study of people with mild cognitive impairment or dementia over 60% reported at least one sleep disorder
  - Sleep disordered breathing (sleep apnea) 60%
  - Excessive daytime sleepiness (50.1%)
  - Insomnia 49.9%
  - REM sleep behavior disorder (22.6%)
  - Restless legs (6.1%)
  - Guarnieri B, Adorni F, Musicco M, et al. Prevalence of sleep disturbances in mild cognitive impairment and dementing disorders: a multicenter Italian clinical cross-sectional study on 431 patients. *Dement Geriatr Cogn Disord.* 2012;33(1):50-58

## Excessive Daytime Sleepiness In Dementia

- Commonly seen in neurodegenerative disorders
- Can occur with or without nighttime sleep problems.
- Can be due to:
  - Environmental (lack of activity or light exposure)
  - Comorbid conditions
    - Depression
    - Sleep disorders
    - Stroke
    - Neurodegenerative disorders
    - Heart disease
    - Head injury
    - Medication-can contribute to worsening cognitive function and increased fall risk

## Circadian Rhythm Abnormalities in Dementia

- Advanced sleep phase syndrome-common as individuals age
- Irregular sleep-wake rhythm disorder can be seen in dementia patients, and may be due to a variety of causes:
  - Patients with irregular sleep wake disorder do not have major sleep periods but rather have 3 or more bouts of sleep during a 24 hour period.
  - Sundowning-worsening behavior, confusion and agitation usually in the evening and night
  - Impaired melatonin secretion
  - Damage to the central body clock (the suprachiasmatic nucleus)
  - Desynchronization of central and peripheral body clocks (such as brain vs stomach clock)
  - Impaired visual input (due to either ocular problems like macular degeneration or due to altered environmental light with being in a nursing home-lack of clear day vs night pattern)

# Dementia and REM Sleep Behavior Disorder

- REM Sleep Behavior Disorder (RBD) is a parasomnia characterized by episodes of vocalization and/or complex movements during sleep.
- Patients with RBD may act out dreams which can sometimes be violent, resulting in injury to the person or bed partner.
- Diagnosed based upon polysomnography or can be based on clinical history and abnormal nocturnal behavior presumed to occur in REM sleep.
- Prevalence is 1%, occurs in 5-13% of community dwelling adults age 60-99.
- Is considered a prodromal biomarker for alpha synucleinopathiesneurodegenerative disorders
  - Parkinson's disease (PD)
  - Lewy body dementia (LBD)
  - Multiple system atrophy (MSA)
- Risk of developing neurodegenerative disease in people with RBD increases over time from 33.5% in 5 years to 96.6% in 14 years.
  - Most develop PD (43%), followed by LBD (25%) and MSA (5%)
- A multicenter study found conversion rate from idiopathic RBD to overt neurodegenerative disorder was 6.3% per year and 73.5% after 12 years of follow up

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## **Obstructive Sleep Apnea (OSA)**

- Obstructive sleep apnea-
  - Affects 900 million people worldwide
  - Defined as repeated physical collapse and blockage of the airway during sleep
  - Can promote not only difficulty with making memory but also can contribute to memory loss
  - One study about obstructive sleep apnea and depression showed sleep apnea patients had more difficulty forming semantic memories(related to personal history), compared to controls (but did not affect the consolidation of episodic memories-those related to events and experiences, to the same extent)
    - OSA causes sleep fragmentation that interrupts the sleep cycle
    - Normal sleep is necessary to consolidate semantic memories
  - Delhikar, N., Sommers, L., Rayner, G., Schembri, R., Robinson, S., Wilson, S., & Jackson, M. (2019). Autobiographical Memory From Different Life Stages in Individuals With Obstructive Sleep Apnea. Journal of the International Neuropsychological Society, 25(3), 266–274.

### Sleep Apnea, Sleep Disturbances and White Matter Abnormalities-p.1

- Recent presentation this April 2023 at the American Academy of Neurology by Dr. Carvalho found:
  - Study results: 140 non-demented participants from the Mayo Clinic Study of Aging who had undergone at least one brain MRI and a polysomnography (PSG) test.
    Participants had a median age of 72.7 years, and 60 percent were men.
  - Older individuals with either severe obstructive sleep apnea or reduced amount of slow wave sleep were more likely to show white matter changes on MRI of the brain.
  - Changes in white matter may be a mechanism by which sleep disturbances could increase the risk of cognitive impairment, dementia, and stroke.
  - It is difficult to know whether sleep disorders cause the white matter changes or vice versa (or if white matter changes causes sleep disorders).
  - White matter changes are a sign of poorer cerebrovascular health.
  - There is no treatment known to restore white matter, so the focus is to find preventive strategies on improving sleep.

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### Sleep Apnea, Sleep Disturbance and White Matter Abnormalities-p.2

- Although many previous studies demonstrated an association between obstructive sleep apnea and cerebrovascular disease, Dr. Carvalho's study is one of the few to also see an association with a reduction in slow-wave sleep.
  - AAN Abstract S6.004: Carvalho D, McCarter S, St. Louis E, et al. Reduced slow-wave sleep and severe apnea are associated with neuroimaging biomarkers of cerebrovascular disease.
- Findings in this study support previous research from 2021
- <u>A 2021 study in *Neurology*</u> reached similar conclusions on the association between reduced slow-wave sleep and adverse brain findings on MRI, including lower cortical brain volume, lower subcortical brain volume, and higher white matter hyperintensities volume.
- Another paper, published in <u>JAMA Network Open in 2022</u>, found that obstructive sleep apnea is linked to not only altered white matter integrity but also changes in sustained attention. That same study also showed that treating obstructive sleep apnea with continuous positive airway pressure significantly improved participants' performance on tests of memory.

## **Obstructive Sleep Apnea (OSA)** and Dementia

- Obstructive sleep apnea is characterized by repeated cessation of breathing during sleep and/or reduction of airflow caused by partial or complete blockage of the upper airway.
- OSA leads to intermittent hypoxia with microarousals or awakenings, causing sleep disruption and excessive daytime sleepiness.
- Inflammation and endothelial dysfunction may ensue and reduce vascular elasticity and increase coagulation, predisposing people to atherosclerosis. Atherosclerosis and reduced oxygenation may cause heart and brain damage.
- Age contributes to OSA with:
  - Higher airway resistance
  - Decreased pharyngeal diameter
  - Increased pharyngeal fat deposits
  - Sleep induced upper airway muscle activity changes

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## **OSA and Dementia Statistics**

- Individuals with Alzheimer's Disease have a 5-fold risk of OSA compared to age-matched controls.
- In a population-based study of people ages 40-85, the prevalence of OSA was:
  - 23.4% in women
  - 49.7% in men
- Prevalence of OSA in people with Alzheimer's Disease is estimated to be as much as 50%.



# OSA and Alzheimer's Disease (AD)Pathology

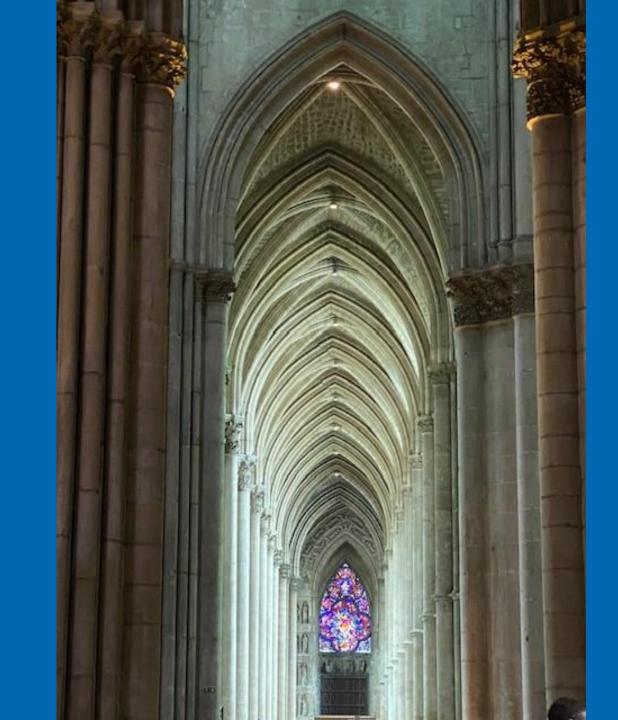
- Patients with OSA have a higher risk of Alzheimer's Disease
- A 3-year pilot study showed that AD patients who were treated with CPAP (continuous positive airway pressure) had significantly less cognitive decline compared to those with OSA that was not treated.
- The increased risk of AD in people with OSA may be due to:
  - Oxidative stress and inflammatory immune responses through intermittent hypoxia
  - Sleep structure changes
    - Disruption of slow wave sleep and REM sleep-causing increases in B amyloid, total tau, and phosphorylated tau production
  - Decreased glymphatic clearance due to high pressure changes during obstructed breathing.
- Increased oxidative stress can lead to endothelial damage and results in increased cardiovascular and cerebrovascular disease.
- Bidirectional relationship between sleep loss and B amyloid aggregation, with sleep loss increasing B amyloid aggregation and that results in further fragmentation and decrease non-REM sleep.

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## Treatment of OSA and Alzheimer's Disease

- Treatment options for OSA include CPAP (gold standard), oral appliance therapy, weight loss, position therapy, and surgical procedures including hypoglossal nerve stimulation (Inspire device).
- An observational study of people with both OSA and memory impairment showed CPAP use for 6 hours per night for 3 months was required to normalize memory performance. Studies of CPAP use in the general population show adherence rates of 40-60%. Of note, Medicare requires use of CPAP for 4 or more hours a night to be considered "compliant" or adherent with treatment.
- Not all cognitive deficits can be normalized however with CPAP use, implying that OSA can lead to some degree of permanent damage to cortical functions.
- Longitudinal studies showed that sustained 1 and 3 year-use of CPAP in people with AD and OSA had positive benefits on cognition and mood compared with those with AD and untreated OSA. Therefore, OSA may be a possible modifiable risk factor for AD.





# Focus on Insomnia

- Definition: A <u>persistent</u> nighttime complaint of:
  - Difficulty falling asleep
  - Difficulty staying asleep
  - Waking earlier than desired
- Associated with:
- Impaired daytime function

# **Types of Insomnia**

Short term insomnia

- Lasts less than 3 months
- Chronic insomnia
  - Occurs at least 3 times a week
  - Has been present for at least 3 months



### Symptoms of Both Short term and Chronic Insomnia

- The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:
  - 1. Fatigue/malaise.
  - 2. Attention, concentration, or memory impairment.
  - 3. Impaired social, family, occupational, or academic performance.
  - 4. Mood disturbance/irritability.
  - 5. Daytime sleepiness.
  - 6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression).
  - 7. Reduced motivation/energy/initiative.
  - 8. Proneness for errors/accidents.
  - 9. Concerns about or dissatisfaction with sleep.

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# **Insomnia and Memory**

- Not getting enough sleep can lower the ability to learn by as much as 40%.
- Sleep deprivation affects how memories are consolidated-not enough time to create new pathways for the information.
- Other potential cognitive effects of reduced sleep include:
  - Trouble learning and focusing
  - Reduced decision-making ability
  - Poor emotional and behavioral control

# On the Flip Side: Excessive Sleep and Memory

- Literature suggests that too much sleep can be associated with cognitive impairment.
- In a study in China with 1,982 older adults, dementia free at the start of the study found that after average follow up of 3.7 years, 97 individuals developed dementia.
- Risk of dementia was 69% greater in those who slept for more than 8 hours (compared to 7-8 hours).
- Risk of dementia also was twice as high in those who went to bed before 9 pm (compared to those who went to bed 10 pm or later)
- The authors suggested that patients who spend prolonged time in bed or advanced sleep timing should be monitored for cognitive dysfunction.
- Reference: "Associations of sleep timing and time in bed with dementia and cognitive decline among Chinese older adults: A cohort study" by Rui Liu, MD, Yifei Ren, MD, Tingting Hou, MD, Ph.D., Xiaoyan Liang, MD, Yi Dong, MD, Yongxiang Wang, MD, Ph.D., Lin Cong, MD, Ph.D., Xiang Wang, MD, Ph.D., Yu Qin, MD, Juan Ren, MD, Shireen Sindi, Ph.D., Shi Tang, MD, PhD, Yifeng Du, MD, Ph.D. and Chengxuan Qiu, Ph.D., 21 September 2022, *Journal of the American Geriatrics Society*. DOI: 10.1111/jgs.18042



### The Dilemma of Too Little or Too Much Sleep

- Insomnia with too little sleep has consequences
  - Cognitive effects
  - Morbidity/mortality-risk of MVAs, psychiatric disturbance (chicken and egg)
- Excessive sleep can also have consequences leading to memory impairment
- Can treatment of insomnia be helpful or harmful?
- Use of sleep aids to improve sleep quality and duration
  - Cons-risk of cognitive effects from medication, risk for falls, potential for physical and psychological addiction, lingering next day effects on attention, risk of MVAs, falls, "dementia"
  - Pros-Improved quality of life, some medications may potentially halt progression or improve memory (to be discussed later!)

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### Hot Topic: Do Sleep Aids Cause Dementia?

- Do sleep aids "cause dementia" or is dementia associated with poor sleep, which in turn results in use of sleep aids?
- Study by Robbins et al in Sleep Medicine 2021 March: 79: 183-189.
  - Nationally representative study age 65+, across 8 years of data, patients screened for dementia, found 15% of older adults routinely use sleep medication (pharmacological and nonpharmacological)
  - They determined that routine use of sleep medication was associated with an increased incidence of dementia over 8 years.
  - The group suggested behavioral strategies over medication as recommended by many national organizations.
  - Limitations to the study-several, important to consider the following:
    - They did not distinguish between medication types and outcomes.
    - They acknowledge that sleep difficulties are a common manifestation in early dementia which may be why people seek medication, and so this may confound the association between sleep medication and cognitive impairment.

# **Insomnia and Dementia**

- 50% of people over age 60 report insomnia symptoms.
- 49.9% of patients with mild cognitive impairment or dementia have a diagnosis of insomnia.
- Insomnia is associated with increased risk of Alzheimer's disease, possibly due to increases in inflammatory response, resulting in increased B amyloid production.
- Sleep is involved in clearance of B amyloid, especially in slow wave sleep.
- Increased time awake and decreased sleep time may affect amyloid clearance, increasing risk of Alzheimer's disease.



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# Insomnia: Prevalence

- Insomnia is the most common sleep complaint in the industrialized world
- Insomnia combined with distress or daytime impairment in roughly 10% of the population
- Transient insomnia symptoms in 30% to 35% of the population





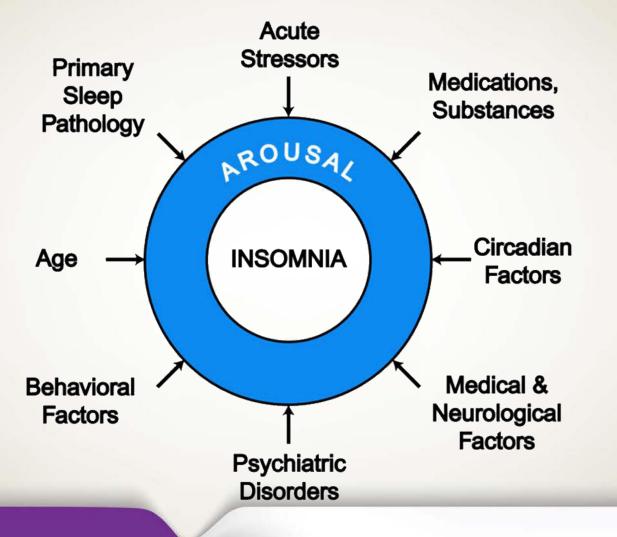
# **Major Risk Factors**

- Previous history of insomnia
  - Habitual "light sleepers"
  - Transient sleep difficulties during times of increased stress
- Increasing age
- Female gender
- Medical symptoms and disorders
- Psychiatric symptoms and disorders
  - Depression
  - Anxiety (particularly about health)
- Socioeconomic status
- Family history



# **Clinical Presentation**

Predisposing, Precipitating and Perpetuating Factors





# **Differential Diagnosis**

- Circadian rhythm sleep-wake disorders
  - Delayed sleep-wake phase disorder
  - Advanced sleep-wake phase disorder
- Sleep-disruptive environmental circumstances (temperature, noise, light, bed partner, hospitalization etc)
- Chronic volitional sleep restriction (Insufficient sleep syndrome)
- Comorbid sleep disorders such as OSA or RLS
- Comorbid medical or psychiatric disorders
- Comorbid with medication use, overuse, or discontinuation



# Insomnia: Consequences

- Decreased quality of life
- Increased healthcare costs
- Increased absenteeism
- Decreased productivity

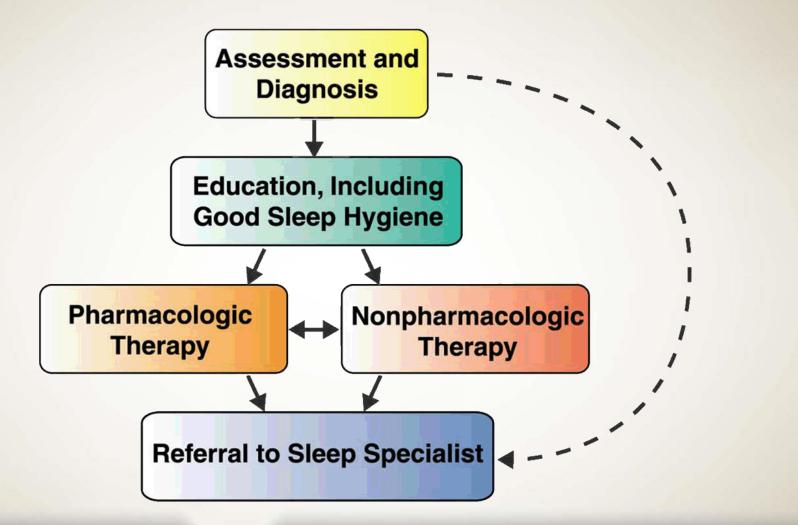


- Increased risk for developing psychiatric disorders
- Increased accident risk

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# Management of Insomnia





# **Assessment: Patient History**

- History of insomnia complaint: onset, frequency, severity, duration, characteristics, some questionnaires can be helpful
- Daytime impairment (e.g. tiredness vs. sleepiness; cognitive difficulties; mood disturbances)
- Sleep habits (24-hour sleep/wake cycle)
- Risks / Precipitating Factors / Perpetuating Factors
- Medical, neurological, and psychiatric history
- Medications
- Other sleep disorder symptoms
- Health habits



 The teaching in Sleep Medicine Fellowship is that if someone has one sleep disorder, they are likely to have more than one sleep disorder.

# **OSA** and Insomnia

- A high prevalence (39%-58%) of insomnia symptoms have been reported in patients with OSA
- Between 29% and 67% of patients with insomnia have an apnea-hypopnea index of greater than 5
- Combination therapy, of CBTI and OSA treatment, resulted in greater improvements in insomnia than did either CBTI or OSA treatment alone



# **RLS** and Insomnia

- Restless legs syndrome is a frequent cause of insomnia; treatment of RLS may improve insomnia
- Comorbidities not only include insomnia, but also depression, anxiety, and pain disorders.
- Some of the medications used to treat insomnia and depression can exacerbate RLS

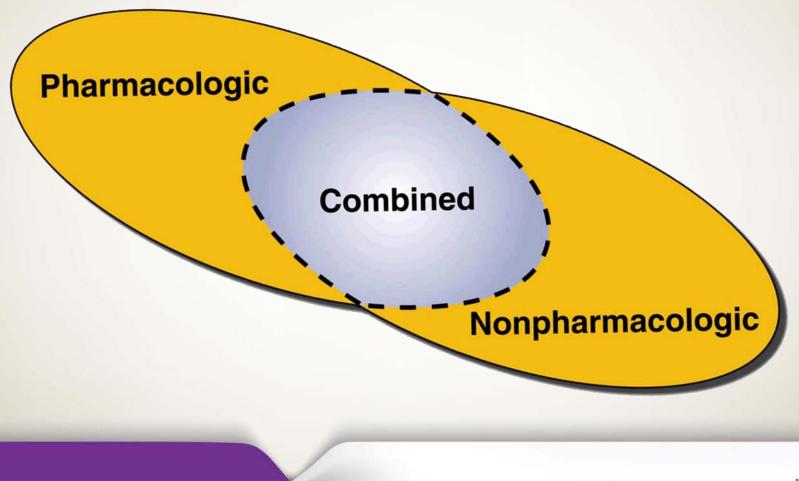


# Medications/substances that can cause insomnia

- Antidepressants
- Stimulants
- Steroids
- bronchodilators
- Decongestants
- Caffeine
- Alcohol



### **Treatment of Insomnia**



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# Treatment

- Treat any co-morbid sleep, medical, neurological, or psychiatric conditions
- Review patient's medication list for potential sleep disruption
- Non-pharmacologic Treatments
  - Cognitive behavioral therapy
  - Exercise
- Medications



# **Cognitive Behavioral Treatments**

TECHNIQUE	AIM		
Sleep hygiene	Promote habits that help sleep; provide rationale for subsequent instructions.		
Stimulus control	Strengthen bed & bedroom as sleep stimulus		
Sleep restriction	Restrict time in bed to improve sleep depth & consolidation		
Relaxation training	Reduce arousal & decrease anxiety		
Cognitive therapy	Address thoughts and beliefs that interfere with sleep.		



# Cognitive Behavioral Treatment: Sleep Hygiene

- Regularize sleep / wake schedule
- Wake up at a consistent time, including weekends
- Avoid stimulants and stimulating behavior
- Establish relaxing bedtime routine
- Provide conducive sleep environment
- Limit daytime naps
- Reduce or eliminate alcohol and caffeine
- Obtain regular exercise
- Avoid clock watching



# Cognitive Behavioral Treatment: Stimulus Control

- Use bed for sleep and sex only
- Go to bed only when sleepy
- Get out of bed when unable to sleep after approximately 15-20 minutes







### Cognitive Behavioral Treatment: Sleep Restriction

- Determine average time asleep based on baseline sleep diary
- Set time in bed = time asleep
- Consistent wake-up time
- No daytime naps
- If time asleep > 85% of time in bed then increase time in bed (15-20 minutes)
- If time asleep < 80% of time in bed then decrease time in bed (15-20 minutes)
- Time in bed increases continue as long as sleep efficiency <a>85% until patient reports optimal daytime functioning</a>

Spielman AJ et al. SLEEP 1987;10.



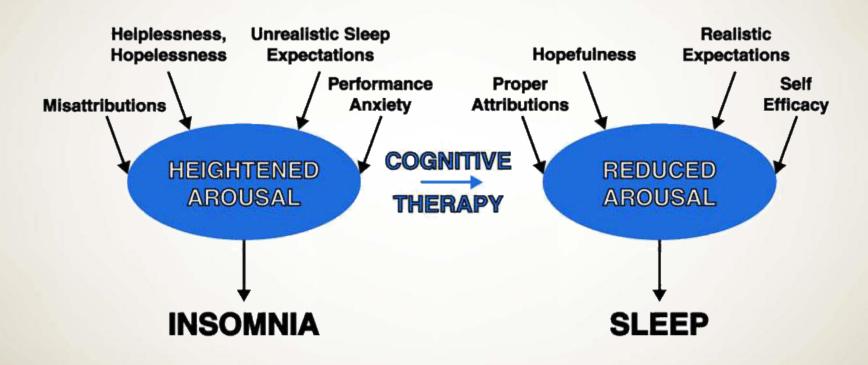
### Cognitive Behavioral Treatment: Relaxation

- Progressive muscle relaxation
- Diaphragmatic breathing
- Meditation and guided imagery
- Biofeedback (EMG)
- Mindfulness





### Cognitive-Behavioral Treatment: Cognitive Therapy



Adapted from Morin CM. J Psychosom Res 1999;46.



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#### Types of Cognitive Behavioral Therapy for Insomnia (CBT-I)Delivery Models

#### Face to face individual CBT-I

- Most ideal (improvement in sleep quality, sleep latency, wake after sleep onset, total sleep time and sleep efficiency)
- 6-8 sessions
- Problem with access to trained clinicians

#### Group CBT-I

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- If individual CBT-I is limited or unavailable
- Improvement in sleep onset latency, sleep efficiency, wake after sleep onset

#### Brief Behavioral Treatment (BBTI)

- 4 brief sessions, two can be phone sessions
- Developed to shorten duration of treatment and due to lack of trained clinicians

#### Computer based CBT-I

- Used when no clinicians are available
- Improvement of sleep onset latency, sleep efficiency, sleep quality, number of awakenings and Insomnia severity index

# Digital CBI-I Efficacy Study JAMA 2023

- Comparative Effectiveness of Digital Cognitive Behavioral Therapy vs Medication Therapy Among Patients With Insomnia
- Menglin Lu, MSC<sup>1</sup>; Yaoyun Zhang, PhD<sup>2</sup>; Junhang Zhang, PhD<sup>3</sup>; et alSongfang Huang, MSC<sup>2</sup>; Fei Huang, PhD<sup>2</sup>; Tingna Wang, MSC<sup>4</sup>; Fei Wu, PhD<sup>1</sup>; Hongjing Mao, MD<sup>1,3</sup>; Zhengxin g Huang, PhD<sup>1</sup>
- Author Affiliations <u>Article Information</u>

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- JAMA Netw Open. 2023;6(4):e237597. doi:10.1001/jamanetworkopen.2023.7597
  - retrospective cohort study was conducted using longitudinal data collected via a mobile app named Good Sleep 365 between November 14, 2018, and February 28, 2022
  - Treatment with dCBT-I, medication therapy, or combination therapy
  - clinical evidence suggested that combination therapy was optimal, and dCBT-I was more effective than medication therapy, with long-term benefits for insomnia management



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# **Pharmacotherapy: Indications**



#### **Acute Stress**



#### **Predictable Stress**



Shift Work / Jet Lag



#### **Chronic Insomnia**



AMERICAN ACADEMY OF SLEEP MEDICINE

# Factors to Consider for Pharmacologic Treatment of Insomnia

- Must individualize treatment/management
- Patient factors:
  - Comorbidities
  - Time of night/pattern of insomnia
- Medication factors:
  - Half life
  - Nightly vs intermittent dosing
  - At bedtime/middle of the night dose timing
  - Side effects
  - Duration of treatment
  - Discontinuation of treatment; potential rebound insomnia
  - Cost

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### Neurotransmitters in sleep and arousal

Facilitate Sleepiness	Facilitate Arousal	
Adenosine	Acetylcholine	
GABA	Dopamine	
Galanin	Glutamate	
Glycine	Histamine	
Melatonin	Norepinephrine	
	Orexin 1 and 2	
Adapted from Gulyani 2012	Serotonin	



# Pharmacotherapy

- Benzodiazepine receptor agonists (includes nonbenzodiazepine and benzodiazepine medications)
- Melatonin receptor agonists (melatonin and ramelteon)
- Orexin receptor antagonists (suvorexant, lemborexant, daridorexant)
- Antidepressants (trazodone, doxepin, mirtazapine)
- Antihistamines (diphenhydramine, hydroxyzine)
- Anticonvulsants (gabapentin, pregabalin)
- Atypical antipsychotics (quetiapine)
- Others (herbs, supplements)



#### Benzodiazepine Receptor Agonists: Pharmacokinetics of Approved Hypnotics

Drug	Onset of Action	Elimination Half-Life (h)	Typical Adult Dosage
Zaleplon®	10-20 min	1.0	5-20 mg
Zolpidem®	10-20 min	1.5-2.4	5-10 mg
Zolpidem CR®	10-30 min	3-4.5	6.25-12.5 mg
<b>Eszopiclone</b> ®	10 min	5-7	1-3 mg
Triazolam®	10-20 min	1.5-5	0.125-0.25 mg
Temazepam®	45-60 min	8-20	7.5-30 mg
Estazolam®	15-30 min	20-30	0.5-2 mg
Quazepam®	15-30 min	15-120	7.5-15 mg
Flurazepam®	15-30 min	36-120	15-30 mg



# **BzRA** Possible side effects

- Daytime Sedation
- Cognitive/motor impairment
- Anterograde amnesia
- Possible Rebound insomnia upon discontinuation
- Parasomnia-Complex sleep related behaviors can occur (night driving, night eating, sleep-sex)
- Tolerance/dependence/abuse/withdrawal at high doses (DEA schedule IV)

# Benzodiazepine Receptor Agonists: Clinical Approach

- Establish correct diagnosis
- Evaluate carefully for apnea, respiratory impairment, organic mental disorders, substance abuse history
- Choose drug with desired pharmacokinetic profile
- Use lowest effective dose
- Monitor side effects (e.g. fall risk, sedation)
- Aim for short-term use
- Consider long-term use in carefully selected patients
- Consider CBT along with pharmacotherapy in chronic insomnia



# Melatonin

- 1.3% or 3.1 million US adults use melatonin based on surveys from 2002-2012 per the National Health Statistics Reports, 2015
- Melatonin use among adults in the US more than doubled between 2007 and 2012.
- Ramelteon, a melatonin receptor agonist, does not affect AHI or oxygenation in mild to moderate OSA

#### **Research Letter**

April 25, 2023

### Quantity of Melatonin and CBD in Melatonin Gummies Sold in the US

Pieter A. Cohen, MD<sup>1</sup>; Bharathi Avula, PhD<sup>2</sup>; Yan-Hong Wang, PhD<sup>2</sup>; et al

≫ Author Affiliations

JAMA. 2023;329(16):1401-1402. doi:10.1001/jama.2023.2296



## Quantity of Melatonin-cont JAMA 4/25/2023

A new research letter published in JAMA reports that 22 of 25 over-the-counter melatonin gummy products were inaccurately labeled, with the actual quantity of melatonin in the gummies ranging from 74% to 347% of the labeled quantity.

# Orexin

- 1998 two research teams independently identified a novel peptide, one group naming it "hypocretin" and the other naming it "orexin."
- Is important in maintaining arousal.

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- Animal models show reduced orexin levels result in symptoms consistent with humans with narcolepsy.
- In humans, narcolepsy is associated with a 90% reduction in orexinergic neurons, affecting both the degree of sleepiness and sleep-wake state stability.
- Two distinct forms or orexin, orexin A and orexin B, which bind to orexin 1 and orexin 2 receptors.
  - Have effects on a complex set of wake promoting brain nuclei
    - Ascending reticular activating system promotes wakefulness
    - Venterolateral preoptic region (VLPO) promotes sleep
- Orexin is not only implicated in regulation of sleep and arousal but also in memory, emotions, motivation, attention, autonomic control, feeding, and energy homeostasis.

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# Dual Orexin Receptor Antagonists (DORAs)

- Exogenous substances that bind to the orexin receptors contribute to wakefulness (therefore a potential role in treatment of narcolepsy).
- Substances that act as an antagonist to orexin receptors promote sleep and help insomnia
- There are now 3 dual orexin receptor antagonists FDA approved for sleep (and more in the pipeline)
  - Suvorexant (Belsomra)-FDA approved August 2014
  - Lemborexant (DayVigo)-FDA approved December 2019
  - Daridorexant (Quviviq)-FDA approved January 2022



# Use of Sleep Medication in the Elderly

#### DORAs (Dual Orexin Receptor Antagonists)

#### Pros:

- Studies on Belsomra (suvorexant), limited safety data but:
  - Appears to be well tolerated in the elderly (age 65 and older)
  - No reported differences in falls compared to placebo
  - No evidence of driving impairment 9 hours after taking the medication at bedtime in healthy volunteers
  - No next day hangover, rebound insomnia, complex sleep related behavior or withdrawal effects, cognitive or motor impairment, anterograde amnesia.
  - No effect on mild to moderate obstructive sleep apnea
- Cons:
  - Drug interaction with CYP3A inhibitors
  - More expensive (recently the DORA medications have become more preferred by some insurance presumably due to the better safety profile in the elderly)
  - Due to its effects on the orexin receptors, there can be side effects with narcolepsy symptoms including cataplexy, sleep paralysis, as well as hypnogogic and hypnopompic hallucinations (hence, these medications are contraindicated in narcolepsy patients).

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# Use of Sleep Medication in the Elderly

- Benzodiazepines and other sedative hypnotic use:
  - Pros:
    - Less expensive than newer agents
    - Fewer drug interactions compared to DORAs
  - Cons:
    - American Geriatric Society (Beer's Criteria) recommends against use of benzodiazepine hypnotics due to increased risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes.
    - Risk of dependence and tolerance.

### Novel Approach with Medication to Possibly Treat Alzheimer's Disease Through Sleep

- Sleep disturbance can be an early sign of Alzheimer's Disease with trouble falling asleep and staying asleep years before cognitive problems such as memory loss and confusion begin.
- Alzheimer's disease involves changes to the brain that disrupt sleep, and poor sleep accelerates harmful changes to the brain (can't clear toxins during slow wave sleep)-a vicious cycle.
- Alzheimer's disease begins when plaques of the protein amyloid beta start building up in the brain. After years of amyloid accumulation, a second brain protein, tau, begins to form tangles that are toxic to neurons.
- Cognitive problems start to occur when tau tangles become detectable.
- Poor sleep is associated with higher levels of both amyloid and tau in the brain.
- Mouse models have shown that better sleep can reduce tau and amyloid so this potential model could have implications of halting or reversing the progression of Alzheimer's disease.

### NEWS FLASH: Suvorexant acutely decreases tau phosphorylation and Aβ in the human CNS. Annals of Neurology. April 20, 2023

- 38 participants ages 45 to 65 and with no cognitive impairments underwent a two-night sleep study.
- Participants were given a lower dose (10 mg) of suvorexant (13 people), a higher dose (20 mg) of suvorexant (12 people) or a placebo (13 people) at 9 p.m. and then went to sleep in a clinical research unit.
- A small amount of cerebrospinal fluid via spinal tap was withdrawn every two hours for 36 hours, starting one hour before the sleeping aid or placebo was administered, to measure how amyloid and tau levels changed over the next day and a half.
- Results: people who had received the high dose of suvorexant, amyloid levels dropped 10% to 20% and levels of a key form of tau known as hyperphosphorylated tau dropped 10% to 15%, compared to people who had received placebo. Both differences are statistically significant. Low dose suvorexant was not different from placebo.
- After 24 hours, the tau protein levels rose but the amyloid level stayed low. A second dose of suvorexant, administered on the second night, sent the levels of both proteins down again for people in the high-dose group.

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### Suvorexant acutely decreases tau phosphorylation and Aβ in the human CNS. Annals of Neurology. April 20, 2023

- Can suvorexant be a sleep aid that provides better sleep, result in less cognitive risk and perhaps treat memory loss?
- Lucey BP, Liu H, Toedebusch CD, Freund D, Redrick T, Chahin SL, Mawuenyega KW, Bollinger JG, Ovod V, Barthélemy NR, Bateman RJ. Suvorexant acutely decreases tau phosphorylation and Aβ in the human CNS. Annals of Neurology. April 20, 2023. DOI: 10.1002/ana.26641

### My Thought-Hypothesis: How Can Medications for Insomnia Help to Prevent of Dementia?

- We know that slow wave sleep is essential for consolidation of memory, can act as a cognitive reserve factor, and can function to clear toxic proteins associated with Alzheimer's disease pathology.
- How do you increase slow wave sleep? What medications do this?
  - J Clin Sleep Med. 2009 Apr 15; 5(2 Suppl): S27–S32. Enhancement of Slow Wave Sleep: Implications for Insomnia James K. Walsh, Ph.D



### Medications That Increase Slow Wave Sleep

Drugs Known to Increase Slow Wave Sleep

Drug	Mechanism of action	Reference
Tiagabine	GAT-1 inhibitor	Mathias et al., 2001 <sup>36</sup>
Gaboxadol	Selective extrasynaptic GABAA agonist	Deacon et al., 2007 <sup>21</sup>
Gabapentin	$\alpha 2\text{-}\delta$ site on voltage-gated calcium ion channels	Bazil et al., 2005 <sup>37</sup>
Pregabalin	$\alpha 2\text{-}\delta$ site on voltage-gated calcium ion channels	Hindmarch et al., 2005 <sup>38</sup>
GHB	GABA <sub>B</sub> /GHB agonist	Pardi et al., 2006 <sup>39</sup>
Ritanserin	Partially selective 5HT <sub>2A</sub> receptor antagonist	Dahlitz et al., 1990 <sup>40</sup>
Eplivanserin	Antagonist of Serotonin Two A Receptors (ASTAR)	Hindmarch et al., $2008^{\frac{22}{2}}$
Mirtazapine	Multiple receptors, including 5HT <sub>2</sub> antagonist	Shen et al., 2006 <sup>41</sup>
Olanzapine	Multiple receptors, including 5HT <sub>2</sub> antagonist	Sharpley et al., 2005 <sup>42</sup>
Trazodone	Multiple receptors, including 5HT <sub>2</sub> antagonist	Mendelson, 2005 <sup>43</sup>

GABA,  $\gamma$ -aminobutyric acid; GHB,  $\gamma$ -hydroxybutyrate; 5HT, serotonin.

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### **Hypothesis: How Can Medications for Insomnia Help to Prevent Dementia?**

- Could there be a combination drug with a medication that enhances slow wave sleep (such as mirtazapine or gamma hydroxybutyrate) and one that increases the brain's ability to clear toxic proteins from the brain (such as suvorexant).
- Future research obviously is needed.



# **Other Sleep Aids**

- Hormone replacement therapy
- Herbal therapies
- Over the counter medications
- Alcohol
- Other prescription medications



# Herbal therapies

- Utilization of plants or plant-derived materials for therapeutic purposes
- For insomnia, commonly tried herbals:
  - Ashwaganda
  - Hops
  - Lemon balm
  - Chamomile
  - Valerian
  - Wuling



# **Common OTC medications for sleep**

FDA Indication for Insomnia	No FDA indication for insomnia
Nytol	Melatonin
Sominex	Tryptophan
Sleepinal	Diphenhydramine hydrochloride
Unisom	Tylenol PM
	Anacin PM
	Nyquil



# **Alcohol Effects on Sleep**

- Intermittent alcohol use can help sleep a little:
  - Decreases sleep latency
- Decreases REM first half of night
- Increases REM later in night
- Produces shallow disrupted sleep later in night, particularly with higher doses of alcohol
- Chronic alcohol use results in poor sleep: increases sleep latency, awakenings and wake time; decreases REM and SWS



### Wine Vending Machine in Germany Who Knew?



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# Pharmacologic Treatment: Approach

- Combine with behavioral strategies
- Select appropriate medication
- Use lowest effective dose
- Use at bedtime (or middle of the night, if indicated)
- Duration of therapy
  - Use as needed for an initial 2 to 4 weeks; reassess for longer use
  - Reduce dose as tolerated
  - Intermittent use may be as beneficial as nightly use
  - Reassess and adjust approach



# **Marijuana and Sleep**

- Although patients anecdotally believe marijuana or CBD helps sleep, this may not necessarily be so.
- Pharmaceutical grade THC studies are controlled in terms of THC/CBD dosing but may not reflect real world use and outcomes, as recreational marijuana contains various compounds that may have effects that are difficult to identify and control for.
- Many cannabis studies are done in cancer patients and other chronic conditions so the outcome of improved sleep may be due to treatment of other symptoms like pain, as opposed to a true effect on sleep.
- Daily cannabis users report more sleep disturbance than intermittent users, although there is some information that short term use may be helpful.
- Cannabis may have tolerance and withdrawal effects.
- Route of administration (inhaled versus ingested) can affect time to peak effect (minutes to hours).
- Cannabis and sleep-need more research to answer the question.

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# Little Castle in the Water on the Reine in Germany



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### Consequences of Poor Sleep in Children

- Tired, irritable
- Lethargic
- Requires prompting for simple tasks
- Reduced concentration and persistence for tasks, ADHD symptoms
- Poorer coordination
- More careless errors in everyday tasks and schoolwork
- Increased emotionally reactive
- Need to carefully screen children for sleep disorders before starting medication therapy to adequately address the etiology of the attention deficit/hyperactivity symptoms.
- Until sleep is optimized in children, treatment for ADHD and support for learning will not be effective.



# Children, Sleep and Cognition-ADHD

• 70% of children with ADHD have problems with sleep.

#### Behavioral sleep problems

- Difficulty initiating and maintaining sleep (Insomnia)
- Not willing to go to sleep (stalling)
- Anxiety
- Delayed sleep phase syndrome
- Sleep onset association disorder (needing a parent or object to sleep)

#### Medically based sleep problems

- ADHD children have a higher risk of a variety of sleep disorders
  - Obstructive sleep apnea (OSA in children with ADHD is 25-30%, compared to 3% general pop)
  - Restless legs
  - Periodic limb movement disorder
  - ADHD medications can result in insomnia

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- We reviewed:
- Making memory and types of memory
- How sleep affects and promotes memory
- Sleep and aging
- Sleep disorders and memory
- Dementias and sleep
- Insomnia and effects on dementia
- Treatment of Insomnia-novel medication approaches
- Children, sleep quality and ADHD

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#### Points:

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- Sleep, particularly slow wave and REM sleep, are essential for memory consolidation.
- Slow wave sleep plays a role in the elimination of waste including toxic proteins in the brain.
- Insufficient sleep and excessive sleep can affect memory.
- Inadequate sleep can lower the ability to learn by as much as 40%.
- Aging is associated with decreased slow wave sleep with decrease in the size of the prefrontal cortex. The less slow wave sleep, the harder it is to process memories.
- Less slow wave sleep, results in decreased time to eliminate toxic brain waste.
- Concept of slow wave sleep as a "cognitive reserve factor"-more slow wave sleep can act as a protective factor against memory decline in people who have a high burden of Alzheimer's disease pathology.

- Sleep disorders that disturb or prevent sleep can result in cognitive impairment and reduced memory function.
- Sleep loss increases beta amyloid aggregation. The more amyloid, the more sleep becomes fragmented and there is a reduction in NREM sleep.
- People with dementia have a high incidence of sleep disorders
- Patients with severe obstructive sleep apnea and also patients with reduced slow wave sleep have increased white matter abnormalities on MRI. Changes in white matter may be a mechanism by which sleep disturbances could increase the risk of cognitive impairment, dementia and stroke.
- Obstructive sleep apnea has been linked to increased cerebrovascular and cardiovascular disease
- Treatment of obstructive sleep apnea can improve memory but only to an extent. There may be permanent damage over time.
- Insomnia impedes memory formation due to lack of consolidation of memory. Cognition is also affected by insomnia with trouble learning and focusing, reduced decision-making ability, and poorer emotional/behavioral control.

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#### 101

- Too much sleep as well as to too little sleep can affect cognition.
- Do sleep aids cause dementia or do people who start to develop dementia develop insomnia, causing them to seek treatment with sleep aids?
- If there is one sleep disorder, there is likely more than one sleep disorder that a person experiences.
- Cognitive Behavioral Therapy-(CBI-I) is better than medication to treat chronic insomnia. Combination CBI-I and medications can also be helpful.
- There are now new pharmacologic agents that can be helpful to treat insomnia. Can they also be useful to improve sleep so as to reduce the levels of amyloid and tau, as a mechanism of preserving or treating memory loss?
- Is there a way to enhance slow wave sleep with medication to improve levels of amyloid and tau, as a way to preserve memory?
- Alcohol is not great for sleep and marijuana may not be as helpful as the general population thinks for improving sleep-jury is still out.

A majority of children with ADHD have sleep disorders. It is important to screen children with ADHD for sleep disorders as the sleep disorder symptoms may mimic ADHD. Otherwise, treating a child for ADHD with ADHD medication will only mask the underlying sleep disorder symptoms and not treat the root of the problem.



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# THE END!

### Thank you for your attention!

