SLEEP AND ITS IMPACT ON AGING

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Objectives:

• Develop a differential diagnosis for sleep complaints in older adult patients.

• Have improved skills in treating insomnia in old age.

• Demonstrate improved understanding of the association between sleep disorders and mortality risk, cognitive decline and metabolic syndrome.

DISCLOSURE
Clifford Singer, MD does have a significant financial interest or other relationship with manufacturer(s) of commercial product(s) and or provider(s) of commercial services discussed in the presentation.
AstraZeneca, Eli Lilly, Forest, Pfizer
Slide 1

**SLEEP AND AGING**

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**Overview**

- Sleep and Aging  
- Sleep Disorders  
- Clinical Approach to Sleep Disorders

Slide 3

**Normal Adult Sleep Histogram**

![Normal Adult Sleep Histogram](image_url)
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Sleep Changes with Age

- No consistent change in sleep requirement
- Less deep sleep
- More awakenings
- More daytime sleep
- Separate bedrooms
- More sleep disorders

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Homeostatic Sleep Drive

- "Hour-glass" effect: the longer one is awake the greater the sleep drive via accumulation of sleep-inducing chemicals
  - Adenosine: accumulates during wake/drives SWS
- Other sleep modulators
  - SHT
  - GABA
  - Sleep-inducing peptides
  - GHRF
  - Cytokines
  - Blood-borne factors: SHT, hormones, cytokines

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Homeostatic Sleep Drive

Fig. 1: Lorz cerebroplastic lining - cerebral calcification in the right side every second day, without any period of wake sleep differing width and height of any measurements.
Slide 7

**Reported Hours Slept**

**Older vs. Younger American Adults**

<table>
<thead>
<tr>
<th>Hours</th>
<th>18-54</th>
<th>55-64</th>
<th>65-74</th>
<th>75-84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week Nights</td>
<td>6.2</td>
<td>6.4</td>
<td>6.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Weekends</td>
<td>7</td>
<td>7.2</td>
<td>7.4</td>
<td>7.6</td>
</tr>
</tbody>
</table>

2003 NSF Sleep in America Poll

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**Aging and Sleep Stages**


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**Chronobiologic Regulation**

- Timing of sleep is influenced by hypothalamic pacemaker
- Suprachiasmatic nucleus (SCN)
  - Circadian pacemaker, “body clock”
  - Drives circadian processes, “gates sleep”
  - Maintained in synchrony with the environment through light exposure (external zeitgeber) and melatonin (internal zeitgeber)
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Chronobiologic Phase Disorders of Sleep

- Normal phase position
- Phase advanced
- Phase delayed
- Can't fall asleep
- Can't stay asleep

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Sleep Drive-SCN Interaction

- Sleep Drive
- SCN Alerting Signal
- Melatonin
- Alertness

- Day
- Night
- Evening
- Reduced by aging

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Sleep Efficiency and Aging

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**Longitudinal Study of Sleep**

<table>
<thead>
<tr>
<th>Mean sleep duration (hours)</th>
<th>Older Adults (n=31)</th>
<th>Younger Adults (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset latency (min)</td>
<td>20.5 ± 10.0</td>
<td>13 ± 7.0</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>79 ± 8</td>
<td>88 ± 6</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>714 ± 43</td>
<td>848 ± 27</td>
</tr>
<tr>
<td>Wake time after sleep onset (min)</td>
<td>115 ± 27</td>
<td>56 ± 11</td>
</tr>
</tbody>
</table>

31 older adults (mean age at baseline = 66.5 ± 8.0) studied at two time points averaging 10 years apart.

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**Prevalence of SDB and PLMS**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger Adults</td>
<td>10%</td>
</tr>
<tr>
<td>Older Adults</td>
<td>50%</td>
</tr>
</tbody>
</table>

SDB = sleep-disordered breathing; PLMS = periodic limb movements in sleep.


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**Alzheimer's Disease**

- MCI/Mild AD
  - Same as age-matched controls
  - Insomnia may be risk factor for cognitive decline
- Moderate
  - More awakenings and daytime sleep
- Late
  - Breakdown of diurnal sleep cycle
  - Deterioration of REM cycle

2. Cricco et al. (2001) *JAGS* 49(9):1185-9
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Sleep in PD

- Sleep-wake disturbances in 60-98% \(^1\)
- Types of sleep disorders in PD:
  - Insomnia
  - Abnormal motor activity & RBD
  - Sleep-related breathing disorder
  - Restless leg syndrome & Periodic leg move.
  - EDS and "sleep attacks"
- Sleep disturbance may be greater in caregiver\(^2\)


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Initial Approach: Diagnosis

<table>
<thead>
<tr>
<th>PARASOMNIA</th>
<th>HYPERSOMNIA/DAYTIME SLEEPINESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivity</td>
<td>Primary insomnia</td>
</tr>
<tr>
<td>Inactivity</td>
<td>Insufficient sleep aspers</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Reminiscence</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Somnambulism</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Restless legs</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Night terrors</td>
</tr>
<tr>
<td>REM Behavior Disorder</td>
<td>Mood and anxiety disorders</td>
</tr>
<tr>
<td>Mood and anxiety disorders</td>
<td>Narcolepsy, rapid eye movements, narcolepsy, restless legs</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>Narcolepsy, rapid eye movements, narcolepsy, restless legs</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>Narcolepsy, rapid eye movements, narcolepsy, restless legs</td>
</tr>
</tbody>
</table>

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Diagnostic Tools

- Sleep Interview
  - How are you sleeping?
  - How much sleep do you get?
  - How much sleep do you need?
  - Do you feel alert most days?
  - Do you take anything to help sleep?
  - Are you legs twitchy or restless?
  - Do you snore or have breathing troubles at night?
- Sleep diary/wrist actigraph/PSG
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Rating Scales

- Pittsburgh Sleep Quality Index\(^1\)
- Sleep Disorders Inventory\(^2\)
- Epworth Sleepiness Scale\(^3\)


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ESS Total Score > 10
without obvious transient cause,
should prompt referral to sleep specialist

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Sleep Log

<table>
<thead>
<tr>
<th></th>
<th>Time in bed</th>
<th>Time out of bed</th>
<th>Sleep quality (1 worst, 5 best)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturday</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunday</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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Primary Insomnia

- Long sleep latency
- Long periods awake during the night
- Feelings of frustration while in bed
- Daytime fatigue, but can't nap
- Anticipation of poor sleep
- Twice as common in women than men

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Insomnia Prevalence by Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-34</td>
<td>14</td>
</tr>
<tr>
<td>35-49</td>
<td>15</td>
</tr>
<tr>
<td>50-64</td>
<td>20</td>
</tr>
<tr>
<td>65-79</td>
<td>25</td>
</tr>
</tbody>
</table>

Mellinger, et al., 1985; Foley, et al., 1995

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Insomnia and Chronic Disease


<table>
<thead>
<tr>
<th>Number of Medical Conditions</th>
<th>None</th>
<th>1-2</th>
<th>3 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>36%</td>
<td>52%</td>
<td>12%</td>
</tr>
<tr>
<td>1-2</td>
<td>30%</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Slide 25

**Insomnia and Mortality in Older Adults**

- Sleep latency >30 minutes: 2.14x greater mortality risk ($p=0.005$)
- Sleep efficiency <80%: 1.93x greater mortality risk ($p=0.014$)


Sleep latencies and efficiencies are controlled for age, gender, and baseline medical burden.

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**Mortality Risk of EDS in Elderly**


<table>
<thead>
<tr>
<th>Relative Odds Ratio</th>
<th>Females: &lt; 1 hr. nap</th>
<th>4.87 (CI 1.22-17.80)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females: 1-2 hr. nap</td>
<td>5.57 (CI 1.05-29.49)</td>
</tr>
<tr>
<td></td>
<td>Males: &lt; 1 hr. nap</td>
<td>0.9 (CI 0.39-2.38)</td>
</tr>
<tr>
<td></td>
<td>Males: 1-2 hr. nap</td>
<td>2.81 (CI 1.01-6.80)</td>
</tr>
<tr>
<td></td>
<td>Males: &gt; 2 hr. nap</td>
<td>13.6 (CI 0.08-2.10)</td>
</tr>
</tbody>
</table>

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**Insomnia: Precipitating Factors**

- Pain
- Depression
- Bout of illness
- Stress and anxiety
  - New born, finances, relationships, etc.
- Menopause
- Environmental factors
  - Noise, temperature, bright light, fear, air travel (jet lag), shift work
Insomnia: Perpetuating Factors

- Psychological conditioning
- Adopting maladaptive sleep habits
  - Tossing and turning, TV on, “night-cap”, cigarette break, coffee break, heavy meal at night, excessive daytime napping, dependence on sedatives
- Chronic health conditions
- Chronobiologic factors

Treatment

BzRAs Approved for Insomnia

<table>
<thead>
<tr>
<th>Name</th>
<th>Half-life (hours)</th>
<th>1.5-5.5</th>
<th>1.5-18.4</th>
<th>3.5-18.4</th>
<th>10-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonata®</td>
<td></td>
<td>47-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambien®</td>
<td></td>
<td>27-43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halcion®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-9</td>
</tr>
<tr>
<td>Restoril®</td>
<td></td>
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<td></td>
<td>10-24</td>
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<td>ProSom®</td>
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</tr>
<tr>
<td>Dalmane®</td>
<td></td>
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</tr>
</tbody>
</table>

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### Bz GABA<sub>A</sub> Agonists

- Benzodiazepines (lorazepam, tamazepine, etc.)
- Zolpidem (Ambien, Ambien CR)
  - Peak level: 1.6 hrs.; T<sub>1/2</sub>= 2.5 hrs.
  - CR approved for chronic use
- Eszopiclone (Lunesta)
  - Peak level: 5-6 hrs.; T<sub>1/2</sub>= 6-9 hrs.
  - Approved for chronic use
- Zaleplon (Sonata)
  - Peak level: 1 hr.; T<sub>1/2</sub>= 1 hr.
- All increase fall risk

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### Rozerem (ramelteon)

- Melatonin receptor agonist
- Non-scheduled hypnotic
- Approved for chronic insomnia
- No signal for tolerance, dependency
- No cognitive or psychomotor impairment
- Safer with COPD/OSA
- Sleep onset latency effect only
- 8 mg dose, cleared by P450 1A2
- Lower rate of response?

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### Off Label Drugs

- Antidepressants
  - Safer with COPD/OSA
- Antihistamines
- Gabapentin
- Quetiapine (Seroquel)
- Gamma-hydroxybutyrate (GBH)
- Melatonin
- Valerian
### Slide 34

**Off Label Agents**

<table>
<thead>
<tr>
<th>SOL</th>
<th>WASO</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td>Reduced</td>
<td>No effect</td>
</tr>
<tr>
<td>Divalproex</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>No effect</td>
<td>Increased</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>GHB</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**Comment**

- SOL = Sleep Onset Latency
- WASO = wake after sleep onset

### Slide 35

**Antidepressants**

<table>
<thead>
<tr>
<th>SOL</th>
<th>WASO</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosepin</td>
<td>reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Trazodone</td>
<td>reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>reduced</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**Comment**

- WASO = wake after sleep onset

### Slide 36

**Cognitive-Behavioral Therapy (CBT)**

- **Cognitive**
  - De-catastrophizing
  - Sleep education
  - Suppression
- **Behavioral**
  - Stimulus control
  - Bed restriction
  - GTB only if tired
  - Do not "try" to go to sleep
  - Exercise
  - Bright light
  - Low caffeine and alcohol
  - Regular sleep times
  - Avoid long naps
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**Combined CBT and Pharmacologic Approaches**

\[\text{WASO (min)}\]

<table>
<thead>
<tr>
<th></th>
<th>CBT</th>
<th>PCT</th>
<th>Placebo</th>
<th>CBT + PCT</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>Pretreatment</td>
<td><img src="graph.png" alt="Graph" /></td>
<td><img src="graph.png" alt="Graph" /></td>
<td><img src="graph.png" alt="Graph" /></td>
<td><img src="graph.png" alt="Graph" /></td>
<td><img src="graph.png" alt="Graph" /></td>
</tr>
<tr>
<td>Post-treatment</td>
<td><img src="graph.png" alt="Graph" /></td>
<td><img src="graph.png" alt="Graph" /></td>
<td><img src="graph.png" alt="Graph" /></td>
<td><img src="graph.png" alt="Graph" /></td>
<td><img src="graph.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

WASO = wake after sleep onset; CBT = cognitive behavior therapy; PCT = pharmacotherapy. Reproduced with permission from Morin et al. JAMA. 1999;281:991-999.

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**Chronobiologic Therapies**

- Melatonin 0.5 mg or Rozerem 8 mg
- CBT and lifestyle changes ± sedative-hypnotic

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**Restless Legs Syndrome**

- Exercise
- Stretching/yoga
- Warm bath
- Dopamine agonists
- Opioids
- Gabapentin
- Sedative-hypnotics
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Depression or Anxiety with Insomnia

- Mirtazapine 7.5-30 mg qhs
- Trazodone 25-150 mg qhs
- SSRI/SNRI plus BzRA or ramelteon
- Consider mood stabilizer if hypomanic

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Actigraphic Sleep in AD

Singer C et al. APS Annual Meeting, June 1997

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Insomnia in Dementia

- Maximize bright daytime light exposure
- Structured daytime activity
- Trazodone or quetiapine for nighttime awakenings associated with agitation
Melatonin for Insomnia in AD
Singer C et al. Sleep 2003; 26:7:893-901

- Only multi-center RCT for AD sleep disturbance in literature
- Placebo, 2.5 SR mel or 10 mg melatonin
- Positive outcome by sleep diaries
- Trend for improved sleep in melatonin group with actigraphy
  - mean 15 minute increase in NTST
  - Underpowered? N = 157

AD Subjects Referred for Insomnia (n = 157)
Singer C et al. Sleep 2003; 7:893-901

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nighttime sleep time</td>
<td>350.5 ± 83.0</td>
</tr>
<tr>
<td>Daytime sleep time</td>
<td>151.2 ± 96.1</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>0.69 ± 0.11</td>
</tr>
<tr>
<td>WASO</td>
<td>162.4 ± 59.4</td>
</tr>
</tbody>
</table>

AD Sleep Disturbance: Is it Wake or is it Sleep?

- Nighttime awakenings
  - 24% caregivers report patient wakes them
  - 70% report this causes moderate to severe distress
- Excessive daytime sleepiness
  - 40% caregivers report that patients sleeps more than usual
  - 38% report this as distressing
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Modafinil and Sleep in AD
Singer C and Nanda F. Annual Meeting Biol Psychiatry, 2007
Patients w AD, n = 16
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AD Caregivers and Sleep
von Kanel et al. JAGS 2006; 54:431-437

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Summary
- Transient insomnia
  - Sleep medication, Rx precipitating problem
- Persistent insomnia
  - Rx underlying problem, sleep medication, CBT
- Chronobiologic insomnia
  - Bright light, ramelteon or melatonin
- Daytime sleepiness or parasomnia
  - Refer to sleep center if ESS > 10
  - Increased daytime activity if feasible

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Resources
- National Sleep Foundation
  - www.sleepfoundation.org
- American Academy of Sleep Medicine
- National Center for Sleep Disorders Research