Aging of Human Sleep and Circadian Rhythms

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Outline

• Basics of sleep
• Age related changes in sleep
• Age related changes in sleep, sleep disorders and co-morbid medical conditions
• Basics of circadian rhythms
• Age related changes in circadian rhythms
• Age related sleep disturbance and consequences for metabolic disease
• Hypnotics and aging
Sleep-Wake Homeostasis

Circadian

Physiological and Neurobehavioral Function
Polysomnography: EEG

Brain waves represent different stages of wakefulness and sleep

- Awake
- Drowsy
- Stage N1 (1)

Theta waves
Polysomnography: Sleep EEG

Brain waves represent different stages of wakefulness and sleep

- **Stage N2**
  - (2)

- **Stage N3**
  - (3&4)
  - (Delta sleep)

- **REM**
Polysomnography: Sleep EEG

- **Awake**
- **Drowsy**
- **Stage N1**
  - Theta waves
  - Sleep Spindle
  - K Complex
- **Stage N2**
  - Theta waves
- **Stage N3 (3&4)**
  - Delta sleep
  - Sawtooth waves
- **REM**
The Sleep Cycle

Alternating states of sleep that occur over an 8-hour time period:

- **NREM**: Non-Rapid Eye Movement; Stages 1-4; ~75% of night
  - Deep Slow Wave Sleep (Stages 3&4)

- **REM**: Rapid Eye Movement; Dreams occur; ~25% of night
  - REM Sleep

Minimum recommended sleep duration for adults: [8 hours]
Sleep Changes Across the Human Lifespan

- Increased WASO
- Decreased Deep Sleep

Ohayon et al. SLEEP, 2004
Original Article

Age-related changes in slow wave activity rise time and NREM sleep EEG with and without zolpidem in healthy young and older adults

Evan D. Chinoy a, Danielle J. Frey a, Daniel N. Kaslovsy b, Francois G. Meyer c, Kenneth P. Wright Jr. a,*

Evan D. Chinoy, PhD
Age Related Reduction in Slow Wave Activity Rise Time (Healthy Aging-Older Adults without Sleep or Medical Conditions)

Chinoy et al. Sleep Medicine (2014)
Age Related Changes in Sleep (Healthy Aging)

- Reduced deep NREM sleep (Stages 3 and 4)
  - Reduced Slow Wave Rise Time and Loss of Brain Region differences
- Increased wakefulness after sleep onset (WASO)
  - Increased number and duration of awakenings

*Reduced sleep drive or ability to respond to sleep drive?*
Factors affecting ability to sleep in older adults

- Primary sleep disorders
- Medical illness
- Medications/polypharmacy
- Circadian rhythm disturbances

Ancoli-Israel, Sleep, 2000;
Ancoli-Israel and Cooke, J Am Geriatr Soc, 2005
Insomnia: prevalence by age group

Large-scale community survey of non-institutionalized American adults, aged 18 to 79 years

Modified from Mellinger, et al., 1985; Foley, et al., 1995
Some medical conditions co-morbid with insomnia

• Pain
  – Arthritis
  – Malignancy

• Neurological Disorders
  – Restless legs syndrome
  – Dementia/AD
  – Parkinson’s disease

• Organ-system failures
  – Angina; Congestive heart failure
  – Asthma
  – Chronic obstructive pulmonary disease
  – Gastro-esophageal reflux
  – Incontinence
  – Benign prostatic hyperplasia

Ancoli-Israel, Sleep, 2000
Sleep problems and heart disease

- Excessive Daytime Sleepiness
  - Heart disease: 22
  - No heart disease: 13
  - OR = ns

- Any Insomnia
  - Heart disease: 57
  - No heart disease: 46
  - OR = 1.99
    (95% CI: 1.29-3.07)

- < 6 hr sleep
  - Heart disease: 20
  - No heart disease: 11
  - OR = 1.70
    (95% CI: 1.12-2.58)

Modified from Foley et al., J Psychosom Res, 2004
Sleep problems and depression

- OR = ns
- OR = 2.44 (95% 1.59-3.73)
- OR = 2.19 (95% 1.16-3.55)

Modified from Foley et al., J Psychosom Res, 2004
Drugs that can contribute to insomnia

• CNS stimulants
• Antihypertensives
• Respiratory medications
• Chemotherapy
• Decongestants
• Psychotropics
• Hormones

• Alcohol
• Caffeine
• Diet pills
• Nicotine
Drugs that cause sedation

- **Hypnotics**
- Anti-hypertensives
- Anti-histamines
- Tranquilizers
- Anti-depressants

Sedating drugs, if taken during the day can cause napping, and might interfere with night time sleep.
Obstructive Sleep Apnea
Smoothed plot (5-year moving average) of the prevalence of an apnea-hypopnea index (AHI) of 15 or greater by age

Prevalence of an AHI ≥15, %

Age (years)

Modified from Young et al., Arch Intern Med, 2002
## Demographics and Symptoms of Sleep Apnea

<table>
<thead>
<tr>
<th></th>
<th>Upper Airway Sleep Apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>male</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>5 &amp; 6 decades</td>
</tr>
<tr>
<td><strong>EDS</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Naps</strong></td>
<td>long &amp; not refreshing</td>
</tr>
<tr>
<td><strong>Alert upon Awakening</strong></td>
<td>no</td>
</tr>
<tr>
<td><strong>Pauses in breathing</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Heavy Snoring</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Diastolic Hypertension</strong></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Morbid Obesity</strong></td>
<td>often</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>progressive</td>
</tr>
</tbody>
</table>
The Internal Circadian Clock
High Circadian Driven Melatonin Levels Represent the Biological Night

Normal Relationship Between Internal Biological Time and Sleep
Sleep Timing and Circadian Changes in Older Adults

- Reduced Circadian Amplitude
- Earlier Clock Hour for Circadian Melatonin Phase
- Awakening at an Earlier Circadian Time Closer to Melatonin Midpoint
- Advanced Sleep Time and Waketime Than Desired
- Shorter Sleep Duration

Cognitive consequences of age related sleep disturbance

• Difficulty sustaining attention
• Slowed response time
• Difficulty with memory
• Decreased performance

• May all be misinterpreted as dementia

Ancoli-Israel and Roth, Sleep, 1999
Ancoli-Israel, Sleep, 2000
Age related changes in sleep and circadian rhythms and metabolic dysregulation and disease
Sleep loss increases energy expenditure. It leads us to eat more than we need, which leads to weight gain.

Ad libitum food intake and insufficient sleep

• Shift of food intake to evening hours
  – ~40% more calories as after dinner snacks
• Men overeat regardless of adequate or insufficient sleep
  – Overeat carbs
• Women show more feeding restraint when obtaining adequate sleep
• Women loose feeding restraint during insufficient sleep and gain weight
  – Overeat carbs and fats

Adequate Sleep following sleep loss

Leads to more healthy dietary choices

(Reduced carbs and fats)

Leads to weight loss/maintenance

Sleep disturbances and chronic disease in older adults
Results of the 2003 National Sleep Foundation
Sleep in America Survey

Daniel Foley\textsuperscript{a,*}, Sonia Ancoli-Israel\textsuperscript{b}, Patricia Britz\textsuperscript{c}, James Walsh\textsuperscript{d}

- 1506 community dwelling 55-84 years old; phone survey
- Obesity and diabetes, were associated with sleep-related problems such as breathing pauses, snoring, daytime sleepiness, restless legs.
The association between sleep duration and obesity in older adults

SR Patel¹, T Blackwell², S Redline¹, S Ancoli-Israel³, JA Cauley⁴, TA Hillier⁵, CE Lewis⁶, ES Orwell⁷, ML Stefanick², BC Taylor⁸, K Yaffe⁹ and KL Stone² for the Osteoporotic Fractures in Men and the Study of Osteoporotic Fractures Research Groups

Wrist actigraphy
5.2 (0.9 SD) nights in 3055 men (age: 67–96 years) participating in the Osteoporotic Fractures in Men Study (MrOS)
4.1 (0.8 SD) nights in 3052 women (age: 70–99 years) participating in the Study of Osteoporotic Fractures (SOF)
Subgroup of 2862 men and 455 women also underwent PSG for OSA
The association between sleep patterns and obesity in older adults

SR Patel¹, AL Hayes², T Blackwell³, DS Evans³, S Ancoli-Israel⁴, YK Wing⁵ and KL Stone³ for the Osteoporotic Fractures in Men (MrOS) and the Study of Osteoporotic Fractures (SOF) Research Groups
3053 men (mean age 76.4 years) and 2985 women (mean age 83.5 years) mean 5.2 and 4.1 actigraphic sleep data days...
Sleep Duration as a Risk Factor for the Development of Type 2 Diabetes

N=1567, Massachusetts Male Aging Study without diabetes at baseline (1987–1989; aged 40-70) were followed until 2004 for development of diabetes

<table>
<thead>
<tr>
<th>Sleep duration</th>
<th>a. Age adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 h</td>
<td>2.60 (1.28–5.27)</td>
</tr>
<tr>
<td>6 h</td>
<td>1.93 (1.06–3.50)</td>
</tr>
<tr>
<td>7 h</td>
<td>1.00</td>
</tr>
<tr>
<td>8 h</td>
<td>1.40 (0.78–2.53)</td>
</tr>
<tr>
<td>&gt;8 h</td>
<td>3.63 (1.79–7.38)</td>
</tr>
</tbody>
</table>
- Use of hypnotics in the general population is estimated to range between 3.5% and 11.7%

- Use in older populations is double that of the general population

**Table 1: Agents Which Promote Sleep by Enhancing Sleep Promoting Systems**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Type</th>
<th>Dose (mg)</th>
<th>t1/2 (h)</th>
<th>GABA Alpha Subunit Binding Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam</td>
<td>BZ</td>
<td>0.25</td>
<td>2–4</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Temazepam</td>
<td>BZ</td>
<td>15–30</td>
<td>8–20</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Estazolam</td>
<td>BZ</td>
<td>1–2</td>
<td>10–24</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Quazepam</td>
<td>BZ</td>
<td>15</td>
<td>25–41</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>BZ</td>
<td>15-30</td>
<td>24–100</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Non-BZ</td>
<td>5–10</td>
<td>1</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Non-BZ</td>
<td>5–10</td>
<td>1.5–2.5</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Zolpidem CR</td>
<td>Non-BZ</td>
<td>6.25-12.5</td>
<td>1.5–2.5</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>Non-BZ</td>
<td>1–3</td>
<td>5–7</td>
<td>$a_1$, $a_2$, $a_3$, $a_5$</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>MT1 Agonist</td>
<td>8</td>
<td>0.8–2.5</td>
<td>N/A</td>
</tr>
<tr>
<td>Melatonin</td>
<td>MT1/MT2/MT3 Agonist</td>
<td>0.3-10</td>
<td>0.6-1.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Effects of zolpidem on age related sleep disturbance during the drugs first half-life (most active time of drug)

<table>
<thead>
<tr>
<th>Percent of Recording Time (%)</th>
<th>Placebo</th>
<th>Zolpidem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>7.7 ± 1.1</td>
<td>5.9 ± 1.0 *</td>
</tr>
<tr>
<td>Stage 2</td>
<td>48.4 ± 5.4</td>
<td>54.1 ± 5.5</td>
</tr>
<tr>
<td>SWS</td>
<td>16.9 ± 5.2</td>
<td>15.8 ± 5.8</td>
</tr>
<tr>
<td>REM</td>
<td>3.0 ± 1.3</td>
<td>3.6 ± 1.3</td>
</tr>
<tr>
<td>Wakefulness</td>
<td>24.0 ± 4.3</td>
<td>20.6 ± 4.2</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>76.0 ± 4.3</td>
<td>79.4 ± 4.2</td>
</tr>
<tr>
<td>Latency to Persistent Sleep (min)</td>
<td>19.0 ± 3.9</td>
<td>13.5 ± 1.7</td>
</tr>
<tr>
<td>Awakenings</td>
<td>6.1 ± 1.0</td>
<td>4.4 ± 0.7</td>
</tr>
</tbody>
</table>

Chinoy et al. Sleep Medicine (2014)
Falls

- > 30% of adults over 65 years fall yearly\(^1\)
- ~25% of fall related injuries require hospitalization\(^1\)
- Falls are the leading cause of injury in older adults\(^2\)
  - > 300,000 fatalities yearly worldwide
  - millions of non-fatal injuries
  - high costs to the patient and society - billions

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Fall Risk Factors

• Biological factors
  – e.g., muscular weakness, impaired vision & cognition
• Environmental factors
  – e.g. slippery surfaces, poorly lit rooms
• Sleep problems
  – Frequency of waking up at night
  – Untreated Insomnia
  – Nocturia
• Use of sleep medications
• Daytime naps
Influence of Zolpidem and Sleep Inertia on Balance and Cognition During Nighttime Awakening: A Randomized Placebo-Controlled Trial

Danielle J. Frey, PT, PhD,* Justus D. Ortega, PhD,† Courtney Wiseman, BA,* Claire T. Farley, PhD,† and Kenneth P. Wright, Jr., PhD*

JAGS 59:73–81, 2011
# Beam Step Offs

<table>
<thead>
<tr>
<th></th>
<th>Young (n=11)</th>
<th>Older (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Wakefulness-Placebo</td>
<td>0 (0%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Sleep-Placebo</td>
<td>1 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Sleep-Hypnotic</td>
<td>3 (27%)</td>
<td>7 (58%)*</td>
</tr>
</tbody>
</table>

**NNH**

**Older** = 1.7 (95% CI 1.4, 2.0)

**Younger** = 5.5 (95% CI 5.2, 5.8)

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*p<0.0083

Frey et al. JAGS (2011)
Time Course of Beam Step Offs

Frey et al. JAGS (2011)
<table>
<thead>
<tr>
<th>Conditions Compared</th>
<th>Outcome Measure, Age Group</th>
<th>Treatment Effect</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sleep-Hypnotic vs Wakefulness-Placebo</td>
<td>Sleep-Placebo vs. Wakefulness Placebo</td>
</tr>
<tr>
<td>Working Memory, Older (n=10)</td>
<td>-4.3 calculations</td>
<td>-0.95 calculations</td>
<td></td>
</tr>
<tr>
<td>Working Memory, Young (n=9)</td>
<td>-12.4 calculations</td>
<td>-6.1 calculations</td>
<td></td>
</tr>
<tr>
<td>Cognitive Speed, Older (n=9)</td>
<td>76 msec longer MedRT</td>
<td>27 msec longer MedRT</td>
<td></td>
</tr>
<tr>
<td>Cognitive Speed, Young (n=9)</td>
<td>126 msec longer MedRT</td>
<td>64 msec longer MedRT</td>
<td>Frey et al. JAGS (2011)</td>
</tr>
</tbody>
</table>
Summary

• Age related changes in sleep architecture and circadian rhythms
  – Reduced sleep drive or ability to respond to sleep drive
• Most sleep complaints endorsed by older adults are not due to aging *per se* but rather to
  – Medical and psychiatric problems commonly seen in the older adult
  – The medications used to treat these co-morbid conditions
  – Higher prevalence of some specific sleep disorders
• Short, variable or disturbed sleep or late sleep timing
  – Contribute to age related metabolic disease
• Current pharmacological treatments for sleep do not produce a young sleep phenotype and have safety risks for aged adults