Sleep Disturbances and Neurocognitive Consequences: An Update

Steven R. Barczi, MD, FAASM
Madison VA Geriatric Research, Education and Clinical Center
UW Division of Geriatrics, DOM
UW Ctr for Sleep Medicine & Research
University of Wisconsin School of Medicine & Public Health
Objectives

- Review the basics of sleep
- Explore associations between sleep, memory and cognition
- Discuss selected causes for sleep disruption in dementia (*e.g.* circadian changes, sleep apnea)
- Highlight several management approaches for enhancing sleep in dementia
Sleep Complaints in Aging

Women >> Men @ all ages

Problems falling asleep ~ 40%
Nighttime awakenings ~ 30%
Early AM awakenings ~ 20%
Daytime sleepiness ~ 20%

Karacan et al, 1976; Vitiello et al, 2004
“Sleep 101”: The Basics

- Essential for life with **multiple key roles** for our brain & body
- Sleep: an **active** process
- Orchestrated by different centers in the brain (hypothalamus, midbrain and brainstem) using multiple neurotransmitters
- Exists as a 24hr biological **circadian rhythm** that is linked to temperature, light and melatonin
- Modulated by external cues, learned behaviors & state of emotional arousal
Sleep - Multiple Essential Roles

- Boost the *immune system*
- Increase *substrate* proteins & clear *CNS metabolites*
- Regulate emotions & *mood*
- Modulate *hormonal processes*
- Enhance learning, *memory* & creativity

Image attribution: https://squarespace.com
Regional glucose uptake is increased in certain areas of the brain in sleep compared to wake state.

Sleep “Drivers”

- Homeostatic sleep drive
- Circadian alerting signal

- Wakefulness Drive
- Alertness
- Alerting Signal
- Process S
- Process C

Timetable:

- 9AM
- 12PM
- 3PM
- 6PM
- 9PM
- 12AM
- 3AM
- 6AM
- 9AM
Ascending Arousal System: The Alerting Signal

LH: Lateral Hypothalamus  PeF: perifornical area  BF: Basal Forebrain  vPAG: Ventral Periaqueductal Grey
TMN: Tuberomammillary Nucleus  LC: Locus Coeruleus  LDT: laterodorsal tegmental nucleus  PPT: pedulopontine nucleus

LH/PeF (orexin; ORX)
BF (Ach)
vPAG (DA)
TMN (Histamine)
Raphe (5-HT)
LC (NE)

Reticular Formation

LH/PeF (orexin; ORX)  BF (Ach)  vPAG (DA)  TMN (Histamine)  Raphe (5-HT)  LC (NE)
Sleep, Cognition and Mood

- Enhancing learning, memory & creativity
- Regulating emotions & mood
- Increasing substrate proteins for the next day's neural activity
- Boosting the immune system
- Modulating endocrine processes (GH, Glc regulation, HPA axis)
Sleep & Memory Processing

- Consolidates declarative memory acquired via hippocampal pathways via reactivation of memory traces (Slow Wave Sleep-SWS)
- Prunes out the “little details” to consolidate the “big picture” - produces context for memory (SWS)
- Strengthens “emotional” memories by reactivating them during sleep
- Enhances memory for motor skills or procedures and “working memory” (REM)
Proteins (orange) that help create connections between neurons build up in the brain while a fly is awake (left) but are depleted after sleep (right), suggesting sleep prunes neural connections, perhaps ensuring only the day’s strongest memories remain.

*Credit: Courtesy of Chiara Cirelli, PhD- UW Ctr for Sleep Medicine & Sleep Research*
Sleep & Memory Processing

• Sleep plays an important role in hippocampus-dependent memory activity

• Deep (slow wave) sleep before learning allows for optimal hippocampal activity and benefits memory encoding


Time- and Sleep-Dependent Improvement on Serial Reaction Time Task
Robertson EM, Curr Biol 2004
The Active System Consolidation Hypothesis

Born J, Physiol Review 2013
Nap-related Memory Consolidation by Age

Recall Performance on Word Pair Recall Task

Hippocampo-Cortical Connectivity by Age

Solid bars represent Nap and hatched bars represent Wake conditions.

Baran B, J Cog Neuroscience 2016
Functional Connectivity in Sleep-related Memory Consolidation

Baran B, J Cog Neuroscience 2016
wakefulness results in a net increase in synaptic strength, sleep with a net decrease

*Tononi and Cirelli 2006*
The Synaptic Homeostasis Hypothesis

Tononi and Cirelli, 2006; Tononi and Cirelli, Brain Res. Bull., 2003

- Synaptic potentiation
- Energy costs
- Space costs
- Saturation
- Energy savings
- Space savings
- Signal / noise

(high SWA) syn
aptic
downscaling

(low SWA) bas
eline

Tononi and Cirelli 2006
Sleep & Regulating Emotions

Functional MRI demonstrates enhanced emotional responses with less prefrontal regulation or "filtering" when we are sleep deprived.

Sleep Changes in Dementia

- 21% to 44% of adults with dementia are reported to have sleep disruption


*Photo Source: Sonia Ancoli-Israel, PhD*
The Consequences of Poor Sleep in Dementia

- Poor sleep in mid-life associated with increased AD in later life. *Osorio 2011, Hahn 2014*
- Shifted sleep-wake activity cycle. *Bliwise 1990*
- Decrement in attention, vigilance, and memory. *Dinges 1997, Yaffe 2014*
- More rapid decline in cognition. *Moe 1995*
The Consequences of Poor Sleep in Dementia

- Increased susceptibility to infection (patients and caregivers) *Ruiz 2012*
- Increased depression in caregivers attributed to sleep deprivation *Wilcox 1999*
- Considerable caregiver distress *Gallagher-Thompson 1992, Gibson 2014*
- Increased placement in institutional settings due to caregiver burnout *Ancoli-Israel 2006, Prince 2014*
Sleep, Brain Changes and Dementia

- The **suprachiasmatic nucleus** (the human circadian pacemaker) degenerates *Videnovic 2014*
- **Subcortical nuclei** that control arousal and sleep deteriorate (basal forebrain nuclei, raphe nuclei, locus coeruleus)
- **Thermoregulatory changes** further disrupt circadian rhythms
In transgenic mice, $A\beta$ levels are higher in the interstitial fluid during wakefulness and lower during sleep, while sleep deprivation increases $A\beta$ concentrations and accelerates plaque deposition.  
*Kang JE, Science. 2009*

In humans, cerebrospinal fluid (CSF) $A\beta_{42}$ also exhibits a diurnal pattern, with the lowest levels occurring in the morning.  *
*Huang Y, Arch Neurol. 2012*

This CSF $A\beta_{42}$ physiological morning decrease is attenuated by total sleep deprivation.  
*Ooms S, JAMA Neurol. 2014*
Sleep appears to promote the functions of the “Glymphatic” system & clearance of metabolites such as AB in animal models during sleep.

Iliff JJ, *J Neurosci* 2014
Diurnal Patterns of CSF Aβ

Huang Y, Arch Neurol. 2012;
N=36 cognitively normal older adults (Mean age 66.8 years)

Methods: clinical and cognitive assessment, a structural MRI, a morning to early afternoon lumbar puncture, and nocturnal polysomnography

Controlled for age, ApoE4

Varga AW, Sleep 2016
Amyloid Deposition & Sleep Changes

Lucey B, Neurobiol of Aging 2014
Summary of Sleep-Wake Disruptions and AD

- Insomnia in mid-life associated with increased risk of pathological changes that precede AD (e.g., CNS increased amyloid burden, neurofibrillary tangles)
- Sleep restriction in mice results in higher AD biomarkers & increases in CNS oxidative stress
- Clearance of Aβ peptides is greatly enhanced during sleep in mice, and awakening the mice disrupts this process
- Patients with impaired cognition and/or increased Aβ burden also show signs of impaired sleep, & animal models have shown that Aβ deposition can directly drive impaired sleep, leading to a positive feedback loop.
Sleep Disruption & Neuronal Death

Cedernaes J, Sleep Med Rev 2016
What do Caregivers say about Sleep in AD?

In 205 community-dwelling AD patients:

- Symptom prevalence-
  - Excessive Sleepiness (40%)
  - Early AM Awakenings (31%)
  - Recurrent Nighttime Awakenings (24%)

- Caregivers were most stressed by nighttime awakenings and reduced total sleep time

*McCurry 1999; Merlino G, Sleep Medicine 2010*
# Sleep Complaints in Dementia

<table>
<thead>
<tr>
<th>Complaint</th>
<th>All Subjects (n=750)</th>
<th>Healthy Subjects (n=644)</th>
<th>Subjects w Dementia (n=86)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia (%)</td>
<td>84.7</td>
<td>85.4</td>
<td>78.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>24.2</td>
<td>25.0</td>
<td>17.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Frequent awakenings</td>
<td>79.8</td>
<td>80.3</td>
<td>76.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Early AM awakenings</td>
<td>25.1</td>
<td>26.3</td>
<td>18.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Snoring/ observed apneas (%)</td>
<td>26.2</td>
<td>26.4</td>
<td>24.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Excessive daytime sleepiness (%)</td>
<td>30.6</td>
<td>29.0</td>
<td>43.6</td>
<td>0.0008</td>
</tr>
<tr>
<td>Tiredness</td>
<td>46.3</td>
<td>45.1</td>
<td>56.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Resistible sleepiness</td>
<td>60.7</td>
<td>60.5</td>
<td>62.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Irresistible sleepiness</td>
<td>29.7</td>
<td>28.1</td>
<td>43.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Sudden sleep attacks</td>
<td>1.4</td>
<td>0.6</td>
<td>7.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Merlino G, Sleep Medicine 2010*
Etiologies for Poor Sleep in Dementia

- Poor Sleep Hygiene
- Primary Sleep Disorders
- Psychiatric and Behavioral Problems
- Illness & Medications
- Circadian Shift
Poor Sleep Habits

- Variable and truncated sleep schedule
- Sustained time in bed (e.g. hospital/ NH)
- Poor bedroom environment (e.g. noise, temperature, clock location etc)
- Excessive daytime napping
- Lack of daytime activity and exercise
- Inadequate sun or bright light exposure
- Caffeine, tobacco or ETOH use
Secretion of Melatonin in Aging

Normal Values in Young Adults 100-120

Melatonin (pg/ml) vs. Time (Hours)

Scholtens RM, J Psychosomatic Res 2016
Sleep Patterns with an Actigraph

- Sleep Phase
- Naps

Control Subject  Time (hrs)  AD Subject
Dementia & Circadian Decay

Adapted from: Ancoli-Israel S. All I Want Is a Good Night’s Sleep. Mosby; 1996
Sleep Apnea and Dementia

- 50%-60% prevalence of SA in dementia
- More severe apneas associated with more severe dementia
- Mild-mod dementia patients tolerate CPAP
- Sleep apnea may (?) be a reversible cause of cognitive loss

Is Sleep Apnea a Cause of “Reversible Dementia” in Old Age?

- OSA studies in the elderly demonstrate mixed findings; cognitive deficits include:
  - Impaired memory for verbal and visuospatial tasks
  - Reduced psychomotor speed
  - Impaired executive function

- The association of cognitive changes is stronger with Apo E4 or co-morbid HTN

Intermittent hypoxia leads to endothelial dysfunction

Exp Physiol 2007;92;51-65
Sleep Apnea & CNS Vascular Disease

Sleep Apnea is associated with the following:

- Insulin resistance
- Increased daytime sympathetic nerve activity
- Systemic inflammation
- Endothelial dysfunction
- Increased oxidative stress

Sleep Apnea and MCI/AD Onset

Osorio RS, Neurology 2015 (ADNI Database)
CPAP Treatment & Dementia

- Limited trials completed to address if CPAP can improve cognition in dementia patients with sleep apnea
- 1 (small) RCT and several descriptive observational studies suggest improvements in episodic memory and executive function. Ancoli-Israel S, JAGS 2008
- CPAP usage produces structural (volumetric) and functional hippocampal changes (4 studies)
### Evidence-based Strategies for Managing Sleep in Dementia

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cognition</th>
<th>Behavior</th>
<th>Sleep/Wake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin/ MT2 Agonists</td>
<td>Improve (2/4 RCTs)</td>
<td>Worse Mood or No Change</td>
<td>Improve (3/6 overall; 2/4 RCTs)</td>
</tr>
<tr>
<td>Cholinesterase Inhibitors</td>
<td>Improve</td>
<td>Improve</td>
<td>Improve (3/5 overall; 1/3 RCTs)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Worsen or No Change</td>
<td>Improve or No Change</td>
<td>Improve (3/4 overall; 2/2 RCTs)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Improve or No Change</td>
<td>Improve or No Change</td>
<td>Improve (1/2- No RCTs)</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>Worsen or No Change</td>
<td>No Data</td>
<td>No Data</td>
</tr>
<tr>
<td>Bright Light Tx</td>
<td>Improve 3/11</td>
<td>Improve 9/15</td>
<td>Improve (10/12 overall; 4/5 RCTs)</td>
</tr>
<tr>
<td>Behavioral/ Multifaceted</td>
<td>No Data</td>
<td>Improve or No Change</td>
<td>Improve (4/5 overall; 3/4 RCTs)</td>
</tr>
</tbody>
</table>

Melatonin Therapy for Sleep in Dementia

- Most randomized-controlled trials show no or modest benefit of Melatonin on sleep or behavior in dementia. 
  
  *Gehrman, Am J Geriatr Psych 2009; Singer, SLEEP 2003*

- Melatonin may have detrimental effects on mood and initiative in dementia. 
  
  *Riemersma-van der Lek, JAMA 2008*
Sleep with Dementia
Medications

- Cholinesterase inhibitors-
  - Aricept 7-10% rates of insomnia; vivid dreaming/ nightmares *Rogers 1998, Burns 1999*
  - Increased REM (dream sleep) *Kamed 2004*
  - Galantamine, Rivastigmine with lower rates of insomnia *Markowitz 2003, McKeith 2000*
  - Dose in AM may be more beneficial for sleep & memory consolidation *Nieoullon 2008*

- Memantine- no published data
Hypnotic Use in Dementia

- Very limited published studies guide our decision-making; None are well designed
- Treatment based on empiricism or collateral evidence (*elderly trials, NH trials, psychotic behavior trials*)
- Rely on global descriptions of sleep (no sleep study data, limited actigraphic data)
An RCT for Trazodone Use in AD

- 30 Subjects with AD were randomly assigned to receive either Trazodone 50mg (n=15) or placebo (n=15) at 10 pm.
- Inclusion criteria: MMSE <24 (mean score=11), Hachinski score <4, sleep complaints on NPI (problems falling asleep, awakenings during night, excessive daytime napping).
- No significant differences in baseline characteristics between groups with age (mean=81 yrs), gender, marital status, education level, depression symptoms, sleep efficiency (by actigraph), nocturnal total sleep time, nap time.

Camargos EF, Am J Geriatr Psychiatry; 2014
An RCT for Trazodone Use in AD

- Treatment group (Trazodone for 2 weeks) showed significant improvements in total sleep time (X=42 min), sleep efficiency (+8%) but no changes in # of awakenings or time awake after sleep onset.

- No differences were noted in caregiver observations of sleep.

- Pre- and Post-treatment measures of Katz, MMSE, Forward/Backward Digit Span, Digit Symbol Coding in both groups did NOT change after 2 weeks.

Camargos EF, Am J Geriatr Psychiatry; 2014
Meta-analysis of Light Therapy on Sleep

Van Maanen A, Sleep Med Rev 2016
## Light Therapy in Dementia

Recent Meta-analysis of 11 high quality studies (4 RCTs) using light tx in dementia with sleep measures as primary outcomes  
*Van Maanen A, Sleep Med Rev, 2016*

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th># of Studies</th>
<th># of Subjects</th>
<th>Effect Size (g)</th>
<th>Q statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Onset Latency</td>
<td>4</td>
<td>48</td>
<td>0.68</td>
<td>5.78</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>8</td>
<td>181</td>
<td>0.36</td>
<td>6.72</td>
</tr>
<tr>
<td>Time in Bed</td>
<td>3</td>
<td>91</td>
<td>-0.39</td>
<td>2.09</td>
</tr>
<tr>
<td>Wake after Sleep</td>
<td>5</td>
<td>128</td>
<td>0.2</td>
<td>10.37</td>
</tr>
<tr>
<td>Early AM Awakening</td>
<td>2</td>
<td>21</td>
<td>0.54</td>
<td>2.04</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>5</td>
<td>115</td>
<td>0.48</td>
<td>6.09</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>4</td>
<td>45</td>
<td>0.78</td>
<td>7.10</td>
</tr>
</tbody>
</table>

Hedges’ g effect size- 0.2 is small, 0.5 is medium, 0.8 is large
Light Treatment on Sleep and Circadian Rhythms in Dementia

- Randomized controlled trial
- N = 77 demented residents in 2 NHs
- Treatment groups (10 day treatment):
  - Evening bright light (2500 lux 5:30 pm – 7:30 pm)
  - Morning bright light (2500 lux 9:30 am – 11:30 am)
  - Daytime sleep restriction (attended to 6 hrs each day by research staff to restrict daytime sleeping)
  - Evening dim red light (<50 lux 5:30 pm – 7:30 pm)
- Wrist actigraphy outcomes:
  - No effects on nighttime sleep or daytime alertness.
  - Significant effects on circadian rhythms of activity

Ancoli-Israel et al. JAGS 50:282-289, 2012
Tailored Lighting in SNF: Effects on Sleep, Agitation and Depression

- Pre- and Post- intervention design using tailored light (low-level “bluish-white light) for individuals with ADRD living in SNF
- N=14 subjects for 4 weeks of light exposure
- Sleep and behavioral measures monitored
  - Daysimeter actigraph for sleep, light/dark & rest-activity patterns
  - Questionnaire data (Pittsburgh Sleep Quality Index, Cohen-Mansfield Agitation Inventory, Cornell Score for Depression in Dementia & MDS-ADL)

Tailored Lighting in SNF: Effects on Sleep, Agitation and Depression

Use of short-wavelength or "blue-enriched" light sources

Tailored Lighting in SNF: Effects on Sleep, Agitation and Depression

**Sleep Efficiency**
- Baseline: 80%
- Intervention: 84%

**Total Sleep Time**
- Baseline: 431 minutes
- Intervention: 460 minutes

**PSQI Global Scores**
- Baseline: 8.7
- Intervention: 4.1
- Post-intervention: 5.3

**CMAI Scores**
- Baseline: 38
- Intervention: 31
- Post-intervention: 32

Daily Social & Physical Activity: Effects on Sleep & Memory

- Controlled trial, N = 23 residents in a continued care retirement facility

- Intervention:
  - Enforced schedule of structured social and physical activity (9 – 10:30 am, 7 pm – 8:30 pm; daily for two weeks)

- Results:
  - Increased slow wave sleep (by polysomnography)
  - Improvement in memory-oriented tasks (by neuropsychological testing)

_Naylor et al. Sleep 23:87-95, 2000_
Behavioral Treatment for Insomnia in Dementia

Nighttime Insomnia Treatment & Education for Alzheimer's Disease (NITE-AD)

- RCT; N=36 (17 w tx, 19 controls) community dwelling pts w dementia and insomnia, and their caregivers
- Intervention: sleep hygiene, daily walking and bright light therapy for 2 months
- Measures: actigraphy, sleep diary, Epworth SSS, Cornell Depression Screen, PSQI
- Results: reduced nighttime awakenings, decreased time awake at night, decreased depressive sxs, increased daytime activity at 2 and 6 months

McCurry J, Am Geriat Society 2005
Key Points

- Sleep is essential for a brain and body
- Sleep plays an important role in memory consolidation
- Sleep disruption may lead to pathology associated with AD/dementia
- Light and behavioral interventions show most promising treatment outcomes (hypnotics and CPAP less clear)
Thank You! Questions?